APRIL 1960
VOL. XXI NO. 4

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

This Issue Includes
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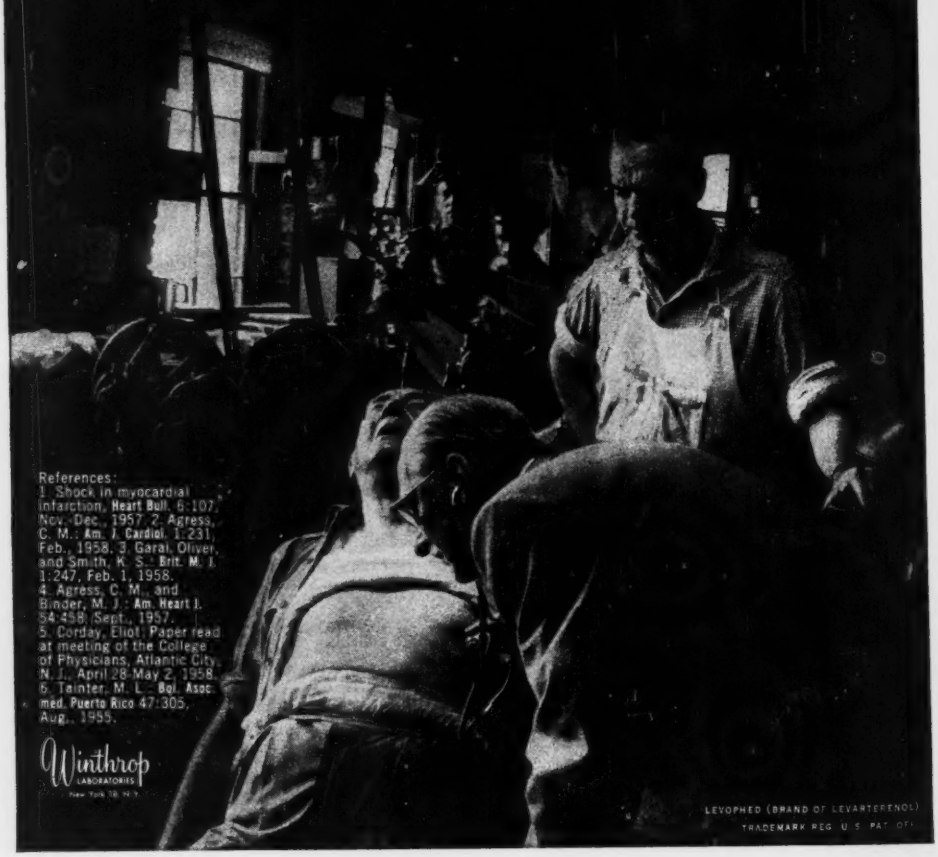

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Circulation
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Editorial

Pediatric Cardiology

THERE have always been obvious differences in central and peripheral cardiovascular phenomena between adults and children and especially infants. It has been necessary for the medical care of children to accumulate normal values illustrating and identifying these differences. Heart rate, blood pressure, and x-ray and electrocardiographic standards still remain incomplete.

Likewise, cardiovascular disease is different in children. Attention for many years has been focused on the developing stages of rheumatic heart disease, and considerable success has been achieved in its prevention, but less study has been applied to the origin or prevention of other types of acquired heart disease. The appearance of disease in an isolated form not associated with aging and degenerative problems makes early or accelerated forms of hypertension or coronary disease especially suitable for study in the child. It seems obvious that the basis for coronary occlusion in young adults must have originated many years previously and that prophylaxis to be successful must be applied early, and perhaps in childhood. This consideration is especially pertinent in children of families with an increased incidence of coronary disease.

The same considerations apply to the study of idiopathic or essential hypertension. The obscure origin of this disease can perhaps be better studied in its preclinical phases, and the slight elevation of blood pressure seen in children during routine examination should not always be ascribed to apprehension. The mechanisms of the hypertensive syndrome are presumably present but relatively unstudied. The early and mild manifestations, while perhaps not significant clinically, lend themselves to study of the uncomplicated disease.

The application of physiologic technics to the study and diagnosis of congenital heart disease associated with central vascular shunts gave strong impetus to interest and effort in laboratories designed and administered for this purpose. In children's hospitals this endeavor tends to focus on congenital heart disease and in general hospitals with both childhood and adult units, this laboratory offers common facilities for the study of a variety of types of circulatory disorders. The application of the new technics for diagnosis even in small infants and uncooperative children has been demonstrated.

Those who devote their full time to the study of the heart and circulation in children and to related clinical and laboratory research believe that pediatric cardiology is a special area of endeavor that will continue to recruit devoted students and practitioners. As this specialty matures and outgrows the initial glamour of its surgical phase and the specialists disperse to practice this new science in

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the communities of their choice, the care of children with heart disease will improve.

The facets of this discipline are varied and include the study of the fetal and newborn circulation, the endless aspects of congenital heart disease, the streptococcal infection and its subsequent kidney and heart disease, and the stimulating opportunity for the study of the origin and prevention of hypertension and coronary heart disease.

While the concept of pediatric cardiology as a career is relatively new, this clinical science also looks to William Harvey as its father: "It will therefore be very useful to look a little more deeply into the matter; to contemplate the movements of the arteries and of the heart not only in man, but also in all other animals with hearts; moreover, by frequent experiments on animals and much use of one's own eyes to discern and investigate its truth."[1]

DONALD E. CASSELS

Reference

1. HARVEY, W.: De Motu Cordis. Translation by Kenneth J. Franklin. Springfield, Ill., Charles C Thomas, 1957.

Michael Servetus

In the *Restitutio* of Servetus, published in 1553 occurs this remarkable passage: "In order, however, that we may understand how the blood is the very life, we must first learn the generation in substance of the vital spirit itself which is composed and nourished out of the inspired air and very subtle blood. The vital spirit has its origin in the left ventricle of the heart, the lungs especially helping towards its perfection; it is a thin spirit . . . generated through the commingling which is effected in the lungs of the inspired air with the elaborated subtle blood communicated from the right ventricle to the left. That communication does not, however, as is generally believed, take place through the medial wall (septum) of the heart, but by a signal artifice the subtle blood is driven by a long passage through the lungs. It is prepared by the lungs, is rendered yellow (light) and from the artery-like vein is poured into the vein-like artery. Then in the vein-like artery it is mixed with the inspired air, and by expiration is cleansed from its fumes. And so at length it is drawn in, a complete mixture, by the left ventricle through the Diastole, stuff fit to become the vital spirit.

"That the communication and preparation does take place in this way through the lungs is shewn by the manifold conjunction and communication of the artery-like vein with the vein-like artery."

Servetus rejected wholly and unreservedly the hypothetical passage of the blood through the septum; he went far beyond the merely hinted scepticism of Vesalius. He had grasped the true features of the pulmonary circulation, the passage of the blood from the right side through the lungs to the left side. He must have attained these results by his own unaided inquiry and thought; and had he given to science the labours which he gave to theology, he obviously might have deserved the title of one of the great anatomists of the time.—SIR M. FOSTER. *Lectures on the History of Physiology.* London, Cambridge University Press, 1901.

The Lewis A. Conner Memorial Lecture

The Performance of the Heart

By LOUIS N. KATZ, M.D.

ONCE AGAIN we are gathered to pay our respects to the memory of Dr. Lewis Atterbury Conner through this lectureship established by the American Heart Association in his honor. This was a fitting act, for Dr. Conner was one of its founders, served as one of its early presidents, and created the first official journal of the Association, the American Heart Journal, of which he was the first Editor. More than this, he played a continuing prominent role in the development of the Association for many years.

I came to know Dr. Conner in the last years of his distinguished career when he had become a legendary figure of the ideal internist and cardiologist. I remember him as tall and upright, reserved and poised, kindly and vigorous—a man one could readily admire. Over a long and active life, he showed by his writings and teachings that he was more than a bedside physician. He was a scholar with a broad interest in all aspects of medicine. It is perhaps significant of his personality that his first publication in 1895, at the age of 28, was entitled "Drifting, Who, How, Whither!" He was interested as much in the public health and psychosomatic aspects of heart disease as in the means of combining history, physical findings, and laboratory data in arriving at a proper diagnosis. Nor was diagnosis an end in itself for him, but rather it was the first step before proceeding judicially to evaluate the existing knowledge in order to manage his patient properly. In short, all aspects of the performance of the heart were his concern.

* * *

This occasion affords me the opportunity to review with you a number of aspects of the performance of the heart with which I have been concerned for many years and to which I have turned once again in the last few years.* Not all phases of the subject will be discussed. Information on the biochemical and enzymatic processes are still too incomplete although some aspects are slowly emerging. This is a challenging aspect that requires intensive investigation in the immediate future.

The similarity of the heart muscle to skeletal muscle in these regards serves as a good starting point. Differences between the 2 muscles do exist, however. Skeletal muscle may have long periods to rest and recover between its bursts of contractions. The heart, on the other hand, beats constantly from before birth until death, and in each diastole it must restore itself completely; otherwise it would not be long before it would be incapable of beating effectively. The heart cannot go into debt, as far as oxygen is concerned, to the extent skeletal muscle can, and it is more vulnerable to hypoxemia. In diabetes mellitus, the heart unlike skeletal muscle shows no sharp decrease in glycogen content nor in its respiratory quotient. The durations of its systole, of its refractory phase, and of its electrical action current are much longer than those of skeletal muscle, and it cannot readily be thrown into a

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The work of the department upon which this lecture is based was supported by the National Heart Institute, American Heart Association, Chicago Heart Association, the Michael Reese Research Foundation, and by a number of private groups and individuals. It is based on studies to which the following have contributed in a major way: Drs. A. Alella, W. Briams, H. Feinberg, A. Gerola, G. Graham, K. Joachim, V. Johnson, A. M. Katz, M. Landowne, D. Laurent, B. Lendrum, M. Mendlowitz, O. Prec, S. Rochard, and W. Wise, as well as Mrs. C. Bolene-Williams, Miss E. Lindner, and Messrs. E. Boyd and F. L. Williams.

Given at the Thirty-second Annual Scientific Sessions of the American Heart Association, Philadelphia, Pa., October 23, 1959.

*Some aspects of the subject have been reviewed recently elsewhere (see Reviews in References).

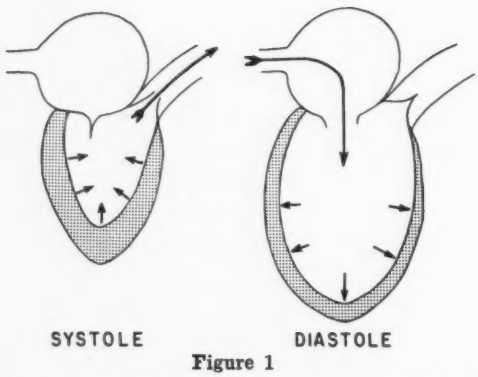

Figure 1

The 2 diagrams show the heart as a compression pump. During systole the ventricle does work by compressing its blood content; during diastole work is done upon the heart by the blood that enters and distends it.

tetanic contraction. These differences indicate significant differences in their chemical and physical performance.

Today, I intend to present 3 aspects of the performance of the heart based on the work done by my associates and myself, at first chiefly on the isolated dog heart and heart-lung preparation, and more recently upon a special open-chest preparation with the heart in situ and subject to the usual neurogenic and hormonal influences. I shall use these data together with the pertinent facts in the literature to extrapolate to the performance of the heart in the unanesthetized animal and in man. Only time and further studies will tell how many of these generalizations will survive. I am aware of the hazards of attempting such an extrapolation but if it serves to stimulate more widespread interest in certain aspects of the performance of the human heart, hitherto somewhat neglected, then it will have been worth the risk.

The Manner by Which the Contractile Effort of the Heart Responds to the Work-Load Imposed upon It

The heart may be conceived as a compression pump. During its systole, the walls of the ventricles compress their content of blood —the work being done *by* the heart muscle (fig. 1). During diastole the blood content of

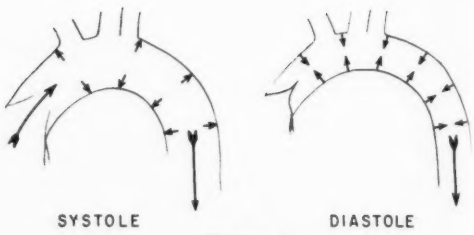

Figure 2

The 2 diagrams show the aorta as a compression chamber. During systole blood from the ventricle distends the aorta, as well as passing through it; during diastole the aorta compresses the blood within it by virtue of its elastic recoil and maintains the onward flow into the periphery.

the ventricular cavities is expanded—the work being done *upon* the heart wall (fig. 1). The possibility that work is done by the heart in diastole, exerting suction on the blood, has been proved, but this effect is small in comparison with the work done by the heart in systole, and special conditions are required for its demonstration. It can therefore be ignored as an aspect of the heart's performance except under certain abnormal circumstances, which as yet are in need of better definition.

Not all of the work done by the heart in its systole is *useful* in the sense either that it is expended in the actual propulsion of blood through the blood vessels in systole, or in building up a pressure head in the aorta and pulmonary artery to make possible continued flow in the blood vessels in the subsequent diastole (fig. 2). The *external useful* work is calculated from the pressure change in the blood expelled (and from the velocity imparted to it) during the ejection.

$$EW = P \cdot V + \frac{m \cdot ve}{2g}$$

EW	=	External work
P	=	Mean arterial pressure during ejection
V	=	Blood volume ejected
m	=	Mass of blood ejected
ve	=	Mean velocity of blood in aorta during ejection
g	=	Gravitational constant

In order better to understand the heart as a compression pump certain of its characteristics should be stressed. It, like other muscles, is a viscous-elastic organ. Alterations of this property help determine how readily it relaxes and contracts. It has one setting when it is fully contracted and another when it is fully relaxed. These can be defined by plotting the pressure-volume relationships of these 2 cyclic states (fig. 3). In the relaxed heart, under steady conditions, the end-diastolic pressure rises with ever increasing magnitude as the end-diastolic volume enlarges progressively. Or, viewed contrariwise, the end-diastolic volume declines by ever increasing increments as the end-diastolic pressure falls. This relationship of end-diastolic volume and pressure defines the *diastolic tone* of a ventricle. A family of such curves can depict changes in diastolic tone, which may play as much of a role as the end-diastolic pressure in determining heart size in diastole (fig. 4).

A similar curve can be constructed for the contracted state with the use of the end-systolic pressures and end-systolic volumes (fig. 3). As expected, the change in viscous-elastic state with contraction is such that pressure in the ventricular cavity is greater in the contracted state than in the relaxed state at any given volume, or, conversely, that for any given pressure, the volume of the contracted ventricle is smaller than when it is relaxed. Without experimental determination, however, the shape of the relationship of end-systolic pressure to end-systolic volume could not be deduced. Actually, the curve is such that the rise of pressure with increasing volume slows progressively until a peak is reached, after which further increases in volume cause the pressure to fall until the systolic curve meets the diastolic one. In the first portion of the curve, the end-systolic volume rises by ever increasing increments as the end-systolic pressure rises, and the volume continues to increase even when the pressure has reached its peak and is again declining. The systolic pressure-volume curve defines what we have called the *systolic tone* of the ventricle, and a family

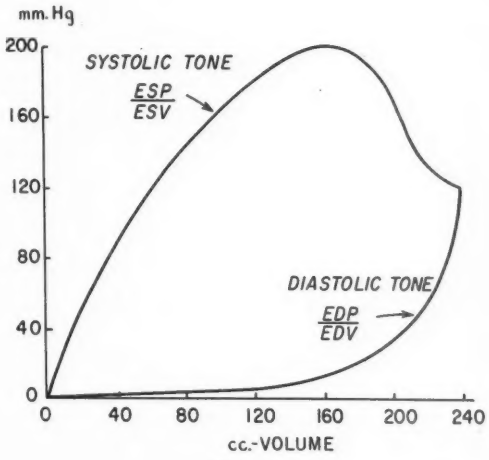

Figure 3

The curves show the volume-pressure relationships of the human left ventricle—extrapolated from known facts. The top curve gives the normal limits attained in the fully contracted ventricle, the bottom one those reached in the fully relaxed ventricle. The former is defined as the systolic tone, *and shows the relationship of end-systolic pressure (ESP) to end-systolic volume (ESV); the latter is defined as the* diastolic tone, *and shows the relationship of end-diastolic pressure (EDP) to end-diastolic volume (EDV).*

of such curves can be constructed that depicts change in systolic tone.

Systolic tone is important, since along with peripheral resistance it determines the residue of blood remaining in the ventricle when contraction is complete, the systolic residue. Evidence is convincing that a ventricle does not empty itself completely, rather the systolic residue is normally about one half the diastolic volume in man and in the closed-chest unanesthetized animal. This systolic residue, together with that volume of blood in the atria, central veins, and lungs, can be called upon in beat-to-beat adjustment of the heart's output according to need above or below the venous return to the heart. This has been overlooked by many in analyzing the heart's performance because conditions are somewhat different in the isolated heart.

The curves of diastolic and systolic tone described above serve as the limits reached by

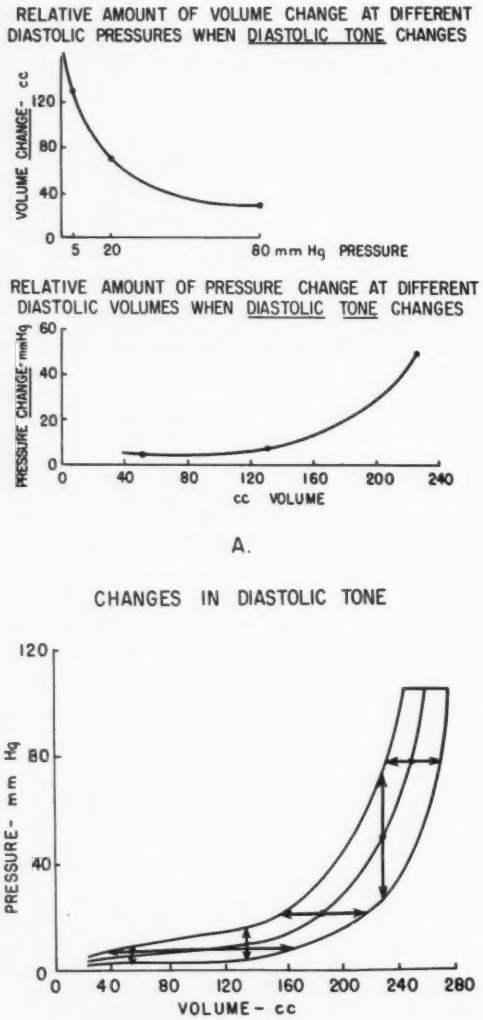

Figure 4

Top. *Segment* A *shows 2 graphs, calculated from segment* B, *showing the amount of diastolic volume change that will occur at different diastolic pressures when an alteration in diastolic tone takes place* (upper curve), *and the amount of diastolic pressure change which will occur at different diastolic volumes when similar alterations in diastolic tone take place* (lower curve). Bottom. *Segment* B *is a reconstruction of the diastolic curve shown in figure 3* (middle line) *with the magnitude of the ordinate increased. The upper curve represents the effect on the diastolic pressure-diastolic volume relationship when diastolic tone increases; the lower one, when the diastolic tone decreases. The horizontal double arrows show the decline in magnitude of the volume change, with a like diastolic tone alteration at constant diastolic pressure, as the intracavity pressure rises—a distended heart shows less volume change than the more empty one. The vertical double arrows show the increase in magnitude of the pressure change, with a like diastolic tone alteration at constant diastolic volume, as the heart size increases—a distended heart shows more pressure change than the more empty one. The importance of these facts on the numerical significance of end-diastolic pressure as an index of end-diastolic volume is apparent.*

the heart in its cycle of contraction and relaxation. How the pressure and volume of the ventricle between these limits change from moment to moment during the heart cycle depends as much on the resistance to emptying in the arteries and the forces in the veins causing filling as upon the moment-to-moment changes in the physical properties of the heart's contractile elements. A work-diagram can be inscribed relating the moment-to-moment changes of pressure and volume—which should be reminiscent of the vector loop of QRS in the frontal plane (fig. 5). Such work-diagrams have been recorded in the isolated cold-blooded and warm-blooded heart, and have been theoretically derived for the intact animal and man (figs. 6 and 7). It is relatively easy to record intracavity pressure accurately by catheterization of the intact animal and man, but such is not the case for ventricular volume. Some approaches to the recording of volume (circumference, cross-section area, or diameter) in intact animals have been made and will doubtlessly be improved and applied in the near future.

With these comments as a background, we are ready to consider the heart's performance. The heart normally is so attuned that it pumps out, over any extended period, as much blood as it receives. In this respect it is no different from the peripheral circulation of the lung and systemic circuits. A number of servomechanisms are involved in this fine ad-

justment of the heart. One of the most important is end-diastolic volume.

End-diastolic volume is determined by 4 independent variables: (1) the systolic residue in the ventricles; (2) the ventricular diastolic tone; (3) the duration of the filling time; and (4) the filling pressure—the mean net difference between the pressures in the atrium and ventricle during the filling phases of diastole.

End-diastolic volume is not the only determinant of the stroke output of the heart. It has been stressed above that changes in systolic residue may independently contribute to the stroke output variations from beat to beat (fig. 7). The contracting and relaxing processes are subject to hormonal and neurogenic influences, as well as mechanical, chemical, and thermal ones, which can change the stroke output independently of their effect via the end-diastolic volume. Recent work in the intact animal shows forcefully that these effects are as important, if not more important, than end-diastolic volume in adjusting stroke output to need. Equally significant is the fact that the minute output of the heart is influenced as much, if not more, by changes in heart rate, as by changes in stroke output. The continued preoccupation exclusively with end-diastolic volume has been a handicap, in my view, to a clear understanding of the character of the heart's performance.

What has been said about stroke output, applies equally well to cardiac external work and oxygen consumption. Even if stroke output were governed exclusively by end-diastolic volume—which it is not—it could not equally govern external stroke-work, since blood pressure, one of the factors in determining work, is set independently of the end-diastolic volume. Actual determinations have shown that both work and oxygen consumption of the heart, even when considered per stroke, vary independently of end-diastolic volume. It is important to stress these facts, since they show that the performance of the heart, whether measured as output, work, or oxygen consumption, is determined by several factors—not just one.

In consideration of the conversion of chemical to mechanical energy, one fact emerges. The ventricular pressure curve is determined not only by the end-diastolic volume but also by other factors. Thus, in each heart cycle, the onset of its pressure rise as well as its contour during ejection, is affected by the arterial resistance existing when ejection begins and that present from moment to moment during this phase. Furthermore, the pressure peak value depends in addition upon the end-systolic volume that is reached, or vice versa.

For completion of this aspect of the subject, it is necessary to deal with the ways by which the heart meets an increase in load, and the effect of this on its reserve. There are 4 mechanisms by which the heart adjusts to loading. These are (1) dilatation, (2) tachycardia, (3) change in its contractile power and distensibility produced by humoral, hormonal, and reflex effects, and (4), when the load is chronically maintained, hypertrophy. These compensatory mechanisms are interdependent; the more there is of one, the less need there is for the others to come into play. It would appear that dilatation, which alters end-diastolic volume along the diastolic tone curve, except when tone changes, comes into play at once. So do tachycardia and change in contractile power. Over any extended period of time, however, hypertrophy takes over and the other compensatory mechanisms abate. It is well known clinically that a patient who has an increased systolic (resistance) load on account of essential hypertension may show no tachycardia or dilatation. The compensatory mechanism drawn upon is hypertrophy, and this for many years may be adequate to meet the increased load. When hypertrophy no longer is adequate, the other mechanisms come into play.

Since there are limits to the extent of these 4 compensatory mechanisms beyond which further increases are detrimental rather than beneficial, it follows that any increased use of these compensatory mechanisms will bring this undesirable turning point closer at hand. Cardiac reserve can be considered to be the difference between the parameter as it exists and the maximum up to which increased per-

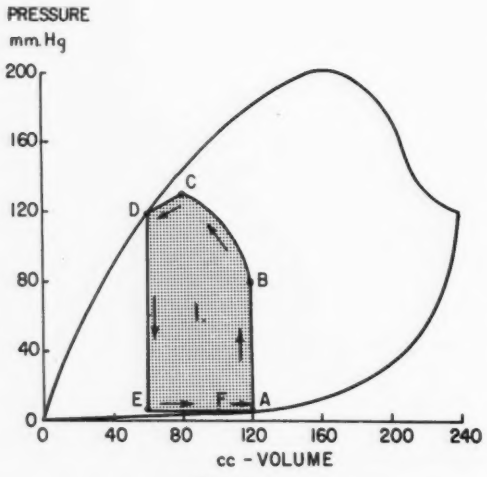

Figure 5

Upon the curves shown in figure 3 is constructed a work-diagram (shaded area—1) *of the ordinary performance of the human left ventricle beating at 80 beats/min., having a stroke-output of 60 ml., a systolic residue of 60 ml., and a blood pressure in the aorta of 130/80 mm. Hg. The arrows show the direction that the pressure-volume changes take during the heart cycle. A-B represents isometric contraction; B-C, rapid ejection; C-D, reduced ejection; D-E, isometric relaxation; E-F, rapid inflow; F-A, diastasis. Work is done from A to D along the arrows by the heart in compressing (and ejecting) blood, and work is done from D to A upon the heart. The area of 1 is an index of the net compression-work done by the heart. This is not the same as the external useful work of the heart. It will be noted that points A and D are, respectively, on the curves of the fully relaxed and fully contracted ventricle, which set the limits of the work-diagram.*

formance of the heart can be expected and beyond which decreased performance ensues. For example, the difference between the existing heart size and the maximum heart size that can augment the heart's performance is one measure of cardiac reserve. An estimate of cardiac reserve would be obtained, if the differences between the existing state and the maximum value beyond which performance declines could be evaluated for each of the following: heart size, heart hypertrophy, heart rate, and cardiac contractile power and distensibility—and the differences then added together. Unfortunately, this is not possible today, useful though it might be.

Time will not permit further discussion of this aspect of the subject. This has been dealt with in extenso elsewhere. It need only be added that significant cardiovascular disease cuts down cardiac reserve not only by increasing the load on the heart—i.e., by raising the resistance, by increasing venous return, or by producing shunts and obstructions—but also by reducing the limits of benefit of the 4 compensatory mechanisms. When compensatory mechanisms approach inadequacy, the heart is no longer equal to the needs of the body and circulatory failure ensues as evidenced by inadequate minute output. At first this will occur during periods of stress, later also during ordinary activity, and ultimately even at bed rest. When the last happens, death will not be far away.

The Factors That Determine the Oxygen Requirements of the Heart as Its Performance Alters

The task of the heart, its external work, as stated earlier, is to propel blood through the arteries during systole and to store blood in them so that flow can continue in diastole. It is of value to the clinician to know the cost of this work in terms of energy expended, particularly since the heart has so small a capacity to go into debt as far as energy is concerned. Oxygen is the best index though a remote one of this energy cost, the cost of mechanical energy in terms of chemical energy. The ratio of external work done by the heart to the energy cost as represented by the oxygen used, in like units, is what is meant by the *external mechanical efficiency* of the heart.

$$ME = \frac{EW}{O_2C}$$

ME = External mechanical efficiency
EW = External work of heart
O_2C = Oxygen consumption of heart

ME is reduced by { decreased minute output / increased heart rate

It is little affected by changes in blood pressure.

Someday we will be able to compare the oxygen consumption with the heat production of the heart and thereby be in a position to relate it to the various chemical reactions going on in the heart at different moments of the heart cycle. It may soon be possible also to relate oxygen use to the heart's high-energy phosphate exchange, which appears to be so intimately linked with the conversion of chemical to mechanical energy.

But even without such detailed knowledge, we know that the heart in situ, subject to its usual hormonal and neurogenic influences, is a pump of low efficiency. Its external mechanical efficiency is such that only one tenth to one seventh of the oxygen used appears in the form of work related to the actual propulsion of blood. In this sense, the heart is a poor pump. But the task of the heart is to gear its machinery so as to adjust blood flow according to need, rather than to do this as inexpensively as possible in terms of energy cost.

The low external mechanical efficiency of the heart cannot be related to the amount of oxygen consumed in maintaining its architecture. This accounts for only 2 ml. per minute, which is about 15 per cent of the rate of oxygen consumed by the heart in its usual state of pumping. It is due rather to the fact that in addition to the *dynamic* effort actually used to propel blood, the heart exerts a large *static* effort (as a compression pump), which is necessary to create and maintain a comparatively high tension in the ventricular walls and a high pressure in their cavities. This we have shown recently by making the left ventricle contract isovolumically, thereby pumping out *no* blood. Under these circumstances, the oxygen consumed by the heart doing *no* external work is of the same order as when it does pump blood. This is not surprising when one considers that no more than one tenth to one seventh of the heart's oxygen consumption is converted to actual external work.

While the external mechanical efficiency is low, it has been found to alter when the conditions of the heart's performance change. And these alterations are of significance to the clinician. The external mechanical efficiency declines when the cardiac minute output is reduced and when the heart rate is accelerated. Alterations in the arterial pressure (the chief factor ordinarily setting the systolic resistance-load) influence the external mechanical efficiency very little per se. It follows from all this that variations in pumping efficiency when external work is altered depend on the accompanying changes in cardiac output, arterial pressure, and heart rate. Thus, with heart rate unchanged, the oxygen cost of an increase in cardiac output (output-work) is little, while for an increase in arterial blood pressure (pressure-work) of equivalent amount, the oxygen cost is large. In short, the change in oxygen consumed by the heart is set not so much by the work it does as by the manner in which work is accomplished.

It is also of significance that when heart rate, cardiac output, and blood pressure are maintained constant in our experiments, severe hypoxia causes the oxygen consumption of the heart to decline, so that utilization of the energy of the heart for propelling blood actually improves. A similar improvement in the external mechanical efficiency of the heart also has been noted by us, on occasion, when the heart has been put under great working stress. There appears to be, under these circumstances, a shifting of gears in the conversion of energy to external work, and such spontaneous improvement in the heart may persist for a matter of minutes or for an hour or so. It is not established whether this is due to the heart making better use of its chemical fuel, or to the heart size being reduced so that wall tension is more effectively converted to cavity pressure, or to the heart making more use of substrates passing to its muscles from the coronary vessels, while, at the same time, the degraded materials are returned to the blood for oxidative restoration elsewhere. However, both the "extreme hypoxemic" and the "stress-adjusting mechanisms" serve the useful purpose of conserving the heart's oxygen supply while maintaining the pumping capacity of the heart

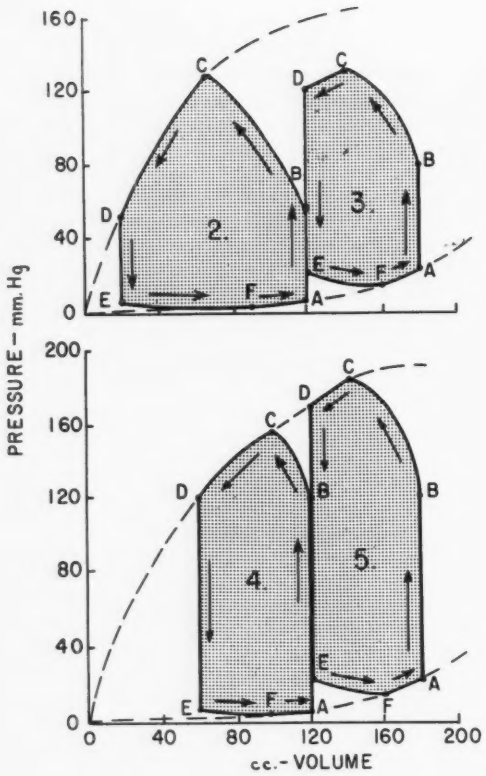

Figure 6

Four work-diagrams of the human left ventricle are shown. These should be compared with the work-diagram in figure 5. The curves depicting the pressure-volume relationship of the fully contracted and fully relaxed ventricle (fig. 3) are shown as dash lines. Work-diagram 2 represents conditions at a heart rate of 48 with the stroke-output 100 ml., and end-diastolic volume 120 ml., the systolic residue 20 ml. and the arterial blood pressure 130/50 mm. Hg. The letters A to F have the same significance as in figure 5. The net increase in compression stroke-work over that in figure 5 is obvious. Work-diagram 3 represents conditions in an incompetent heart without tachycardia (heart rate of 80) and in which the systolic tone has declined, as shown by the fact that D marking the end of systole does not reach the dash-line of the normal systolic tone. The effect of this decline in systolic tone is to increase the systolic residue of the heart to 120 ml. (an increase of 60 ml. over the normal). Compensation, to maintain a stroke output of 60 ml. (and a minute-output of 4.8 L.), is accomplished by Starling's law along the normal diastolic tone curve. The result is that the end-diastolic pressure is 20 mm. Hg. The arterial pressure remains unchanged, 130/80 mm. Hg. In this case the net compression stroke-work has declined compared to curve 1 in figure 5—even though the external useful stroke-work is unchanged. Work-diagram 4 represents conditions in longstanding arterial hypertension in which ventricular hypertrophy has compensated adequately for the increased systolic resistance-load. The heart rate is 80, the heart is not dilated—its end-diastolic volume is 120 ml. The stroke output is normal at 60 ml. The arterial pressure is elevated to 155/120 mm. Hg. The net compression stroke-work is increased with respect to curve 1 in figure 5. Work-diagram 5 represents conditions in early arterial hypertension in which the compensatory mechanism is dilatation, not hypertrophy as in curve 4. The end-diastolic volume here is 180 ml. The stroke-output has been maintained at 60 ml. by virtue of Starling's law, but the systolic residue has doubled to 120 ml. from the normal value of 60 ml. (curve 1, fig. 5). The heart rate is still 80 and the arterial pressure is 180/120 mm. Hg. The difference in compensatory mechanisms for the arterial hypertension in work-diagrams 4 and 5 is worthy of note.

just when this conservation is most needed under the stimulus of oxygen lack or an excessive load.

The fact that external work accounts for such a small proportion of the energy exchange of the heart has led us to seek some other index that might correlate better with the oxygen consumed by the heart. Our first thought was, of course, to seek correlation with each of the parameters entering into the determination of the performance of the heart, namely minute cardiac output, arterial blood pressure, and heart rate. A comparison was therefore made of the effect of each of these 3 variables on the cardiac oxygen consumption. It soon became clear that the relation between minute cardiac output and oxygen consumption was a very poor one, while that between arterial blood pressure and cardiac oxygen consumption was good. Furthermore, an equally good correlation was found to exist between heart rate and oxygen consumption. It seemed natural, therefore, to correlate the oxygen consumption of the heart with the product of arterial blood pressure and heart rate—this we have designated as the

BP × *HR index* of cardiac oxygen consumption. Cardiac output was ignored.

$$\frac{\textit{CARDIAC } O_2 \textit{ CONSUMPTION}}{BP \times HR}$$

is a constant when work-load alters.

BP × *HR* is an index of cardiac O_2 consumption.

This *BP* × *HR index* was found to parallel the oxygen consumption of the heart in our preparation over a wide range of blood pressures (50 to 180 mm. Hg), heart rate (30 to 180 per minute), and cardiac outputs (½ to 2 liters per minute). It also applied over a wide range of blood oxygen and carbon dioxide contents and hydrogen ion concentrations, also when the heart was cooled to 27 C. (ordinary hypothermic conditions). It was found to apply also in the isovolumically contracting heart preparation where no external work was done, *BP* in this instance being determined from left ventricular pressure. So far, only 3 conditions have affected the quantitative relation of the *BP* × *HR index* to the cardiac oxygen consumption. These are marked hypoxemia, exhibition of catecholamines, and sometimes undue stress.

Further work along these lines needs to be done, since this is, at best, only a crude index. There are several reasons for this crudeness. In the first place, it would be better to obtain *BP* from some parameter of the ventricular pressure curve rather than from the arterial pressure, perhaps the best would be the mean pressure of the ventricular pulse or of its systolic portion. In the second place, it is logical to assume that oxygen consumption would be more nearly related to cardiac wall tension than to cavity pressure—the 2 not being synonymous. Wall tension determines cavity pressure and vice versa, but their quantitative relation is set by surface area of the cavity and by the curvatures of its boundaries. In the simplest terms: $P = T/A$ where P is cavity pressure, T is wall tension and A is the area of the cavity surface. Thus, as the heart becomes larger, intracavity pressure becomes a smaller proportion of its wall tension. That wall tension is a better index of cardiac oxygen consumption than is intracavity pressure is shown by the fact that multiplying the *BP* × *HR index* by the cube root of the heart's volume improved the correlation between the index and the cardiac oxygen consumption in the isovolumically contracting heart. The relation between wall tension and cavity pressure has been known for a long time, and has been precisely defined mathematically as the Laplace law.

The fact that changes in cardiac oxygen consumption appear to be mirrored by the *BP* × *HR index,* however crudely, is of value to the clinician, since both mean blood pressure and heart rate are readily determined at the bedside. He has, therefore, easily at hand some idea of the cardiac oxygen consumption in different states of the heart. If used with proper caution and with due regard to its limitations, this *BP* × *HR index* may help his thinking. In the coming years, it will, I am sure, be given further examination and its nature will be changed to give a better index as it undergoes the test "by fire."

How the Oxygen Needs of the Heart Are Met by Adjustments in Coronary Flow and in the Rate of Oxygen Extraction

In order to complete this picture of the heart's performance, consideration must be given to the way in which the oxygen requirements of the heart are met. In the following discussion only steady states will be considered. It would take us too far afield to present the more complicated situation existing while the heart is adjusting to a new steady state. Consideration will be directed to 2 aspects: (1) adjustments when the composition of the blood is altered, and related problems, and (2) the changes that occur under control or abnormal circumstances when the work-load is modified.

First off, it is well known that the oxygen capacity of the myocardium is very small and its oxygen debt low. Hence, it is essential that oxygen be supplied by the coronary vessels quickly as needed. It is, therefore, not surprising that the amount of oxygen available to the heart is readily adjusted to its consumption.

$\frac{O_2\ AVAILABILITY}{O_2\ CONSUMPTION}$ is a homeostatic constant when work-load alters.

It is not altered by hypoxia. It is by acidemia, hypercapnia, catecholamines, and, sometimes, by undue stress.

$O_2\ AVAILABILITY$ = arterial O_2 content × coronary flow.

$O_2\ CONSUMPTION$ = coronary flow × coronary A-V O_2 difference.

This is a homeostatic mechanism whose nature needs to be discussed. This adjustment means primarily that the coronary flow rate is closely linked in a quantitative fashion with the rate of oxygen consumption of the heart—and the factors that alter the latter also simultaneously affect the former and to a like extent. This is apparent when the work-load of the heart changes. Thus, coronary flow adjustments are apparently little influenced by blood pressure except insofar as the latter modifies cardiac oxygen consumption. Apparently, intravascular and extravascular forces acting upon coronary flow balance each other rather closely.

The coronary flow is so finely attuned that it keeps the oxygen available to the heart almost precisely constant in relation to the oxygen being consumed by it. When the arterial oxygen content declines as in hypoxemia, and presumably in anemia, it is found that the coronary flow rate is augmented in an amount that still maintains the oxygen available to the heart attuned to the oxygen it consumes in a given time.

$\frac{CORONARY\ FLOW}{CARDIAC\ O_2\ CONSUMPTION}$ is a homeostatic constant when work-load alters.

It is altered by hypoxia, also by acidemia, hypercapnia, catecholamines, and sometimes, by undue stress.

These adjustments of coronary flow to oxygen need are paramount and supersede or are imposed upon all other kinds of adjustments in coronary flow. This must be appreciated thoroughly by the clinician in his day-to-day handling of cardiac cases. Only when the responsive elements of the coronary vessels became diseased and cannot adjust properly, or when occlusion of a major coronary vessel makes these adjustments of the bed inoperative, does the beautifully attuned, fine adjustment of the coronary flow to oxygen consumption break down.

We have found, however, that hypercapnia, acidemia, and catecholamine exhibition shift this fine adjustment. In these instances, the coronary flow is augmented and the oxygen available to the heart is thereby increased. However, this does not prevent coronary flow and oxygen availability rates from continuing to adjust as before to the rate of oxygen consumed, when the latter varies with work-load alteration, even when the ratios (coronary flow/oxygen consumption) and (oxygen availability/oxygen consumption of the heart) have been shifted from their control values. A similar shift, and in the same direction occurs when the "stress-adapting mechanism," mentioned earlier, appears.

It is important to reemphasize that the adjustments of coronary flow to the oxygen needs of the heart are of paramount importance. They are far more powerful than the mechanical factors to which so much attention has hitherto been paid. They represent, as mentioned, a homeostatic mechanism of prime importance. It may be stated categorically that in evaluating the benefit of any drug or procedure upon the coronary flow rate, any simultaneous effect upon the rate of oxygen consumption of the heart must first be ascertained. Only those drugs or procedures that improve coronary flow alone, or at least improve it out of proportion to their augmenting effect on the oxygen consumed by the heart, can be considered of value for the relief of coronary insufficiency. (Of course, drugs or procedures that lead to a decline of the oxygen needs of the heart are also useful.) Regrettably, this kind of evaluation has not been carried out often enough in the past.

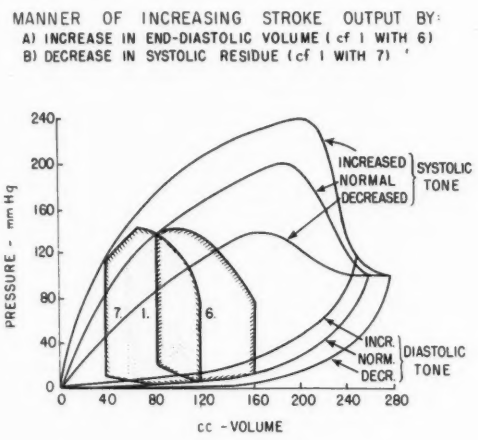

Figure 7

This diagram represents 3 things. First, it shows the alteration in the end-diastolic pressure-volume curve when the diastolic tone changes in the left ventricle of man. Second, it shows the alteration in the end-systolic pressure-volume curve when the systolic tone changes. It can be seen that a family of curves can be drawn on either side of the normal (norm.) to show increase (incr.) and decrease (decr.) of tone. Third, 3 work-diagrams are drawn to illustrate 2 ways by which stroke-volume may be increased. Work-diagram 1 is the normal and reproduces curve 1 in figure 5. Work-diagram 6 shows what happens when the end-diastolic volume increases from 120 to 160 ml. The result is an increase in stroke-output to 80 ml.; the systolic residue rising from 60 to 80 ml. The increase in end-diastolic volume effect is an expression of the Starling law. It is associated with a rise in the end-diastolic pressure along the normal diastolic tone curve. Were the diastolic tone to decrease, a similar rise in end-diastolic volume might occur with less, with no, or with an actual decline in end-diastolic pressure depending on the amount of decline in diastolic tone. That is why end-diastolic pressure is not a necessary index of end-diastolic volume. Work-diagram 7 shows how an increase in stroke-output of a degree similar to that caused by the shift from work-diagram 1 to work-diagram 6 can take place without any change in end-diastolic volume. It can be seen that the end-diastolic volume is identical (120 ml.) in work-diagrams 1 and 7. The increase in stroke-output from 60 to 80 ml. occurs in this case because the inotropic properties of the ventricle are augmented, its systolic tone is increased thereby, and as a result its systolic residue declines from 60 to 40 ml. In this case, therefore, the increased stroke-volume occurred by encroachment upon the systolic residue. The Starling law was not invoked. This cycle of events can continue indefinitely as long as the systolic tone of the heart is enhanced. This figure epitomizes the newer trends in our views on the performance of the heart.

The only other way by which the oxygen supplied to the heart can be varied is by alterations in the amount of oxygen removed from each unit of blood passing through the coronary capillaries, the A-V oxygen difference. This is usually expressed as a ratio, A-V oxygen difference/arterial oxygen content, known as per cent oxygen extraction. The per cent oxygen extracted by the heart is greater than in most organs, so that coronary venous blood contains less oxygen than do the venae cavae, or most other veins.

> *CORONARY A-V O_2 DIFFERENCE* and *CORONARY VENOUS O_2* content are constant when work-load alters.
>
> They are reduced by hypoxia.
>
> *CORONARY A-V O_2 DIFFERENCE* is also reduced by acidemia, hypercapnia, catecholamines, and, sometimes, by undue stress, but *CORONARY VENOUS O_2* content goes up.

The coronary A-V oxygen difference and, with it, the coronary venous oxygen content were found to remain constant over a wide range of the heart's performance so long as the stress was not excessive and the arterial blood oxygen and carbon dioxide contents and the hydrogen ion concentration remained normal. All the adjustments seem to reside in modification of the coronary flow rate. This *is*, one must reemphasize, a remarkable homeostatic mechanism.

The coronary A-V oxygen difference (and coronary venous oxygen content) are not constant under all circumstances. As mentioned earlier, arterial hypoxemia leads to a decline in the coronary A-V oxygen difference. In this state the coronary venous oxygen content falls less than the arterial. Actually, the per cent of oxygen extracted by the heart has been found to remain constant in hypoxemia, apparently because the increase in coronary flow is so nicely attuned as to keep the oxygen

available to the heart constant. Only when the hypoxia becomes excessive will this adjustment become inadequate—and soon the heart's power will decline.

In hypercapnia, acidemia, and catecholamine exhibition, a decline in coronary A-V oxygen difference also accompanies the augmentation of coronary flow. But unlike hypoxia, the coronary venous blood oxygen content rises—that is the venous blood from the heart muscles becomes arterialized. This also occurs in the "stress adapting mechanism." Obviously, the adjustments to these conditions are different from those due to hypoxia or to a change in work-load. The adjustments to work-load and hypoxia may be considered basic, while these other adjustments are superadded as refinements under certain unusual conditions.

It would take us too far afield to enter into the intriguing question of how and by what mechanisms the adjustments of coronary flow and oxygen extraction occur. They are doubtlessly different in the various circumstances. In each case it is necessary to settle whether it is the oxygen extraction or the coronary flow that is primarily altered, or whether both are changed simultaneously. This is an intriguing subject—but I have talked long enough.

* * *

In concluding, I would like to emphasize that this presentation is one man's view of the present status of some significant aspects of the heart's performance. The views expressed are not those that I held 30 years ago, 20 years ago, or even 10 years ago (as a perusal of previous reviews will show) and, I am sure, they will not be the same 10 years hence. As more thought and study continue in this area, concepts will change, approaching, over the long pull, closer and closer to the ultimate truth. Analysis of the heart's performance is an exciting occupation, and I hope I have been able to get across to you some of the things that make it so fascinating to me.

Summario in Interlingua

Isto es le discurso memorial, presentate in honor de Lewis A. Conner, al occasion del trenta-secunde session scientific annual del Association Cardiologic American a Philadelphia, Pennsylvania, le 23 de octobre 1959. Le autor discute 3 aspectos del performance del corde, basante se super recercas effectuate initialmente super toto in le isolate corde e preparato de corde e pulmon del can e plus recentemente etiam in preparatos special a thorace aperte con le corde in sito e exponite al usual influentias neurogene e hormonal. Le datos assi colligite es supplementate per alteres ab le litteratura e usate como base de extrapolationes con respecto al performance del corde de canes intacte e etiam de sujectos human. Le 3 aspectos del thema que es principalmente tractate es: (1) Le maniera in que le effortio contractile del corde responde al carga de labor imponite super illo; (2) le factores que determina le requirimentos oxygenic del corde quando su performance es alterate; e (3) le maniera in que le requirimentos oxygenic del corde es satisfacite per adjustationes del fluxo coronari e del intensitate del extraction de oxygeno.

Le autor sublinea in conclusion que le opiniones presentate es le sues como rececreator individual e que ille mesme non considera los como definitive e absolute. Trenta e 20 e 10 annos retro, le opiniones del autor non esseva illos exprimite per ille al tempore presente, e un simile disveloppamento debe esser expectate in le futuro. In tanto que le studios e le pensar in iste area continua, nostre conception del problemas va cambiar pro approchar de plus in plus—secundo le spero e le conviction del autor—le ultime veritate.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Roentgen Ray. The discovery of the X-ray was announced at a meeting of the Physico-Medical Society in Würzburg in 1895. The paper by Wilhelm Konrad Roentgen (1845-1923), entitled "A New Ray" *(Uber eine neue Art von Strahlen)* appears in the *Sitzungsberichten der Würzburger Physik-medic, Gesellschaft,* 1895, pp. 132-141.

"If in a completely darkened room, one allows the discharges from a large Ruhmkorff coil to pass through a Hittorf vacuum tube (or a sufficiently evacuated Lenard's, Crookes' or other similar apparatus) and covers the tube with a rather closely fitting jacket made of thin black cardboard, a paper screen which has been painted with barium platinum cyanide will be seen to glow brightly and become fluorescent when brought near the apparatus. It makes no difference whether the painted or the unpainted side of the screen is turned toward the source of the discharge. . . . In the presence of this phenomenon one is first struck by the fact that some agent is passing through the black cardboard jacket—a jacket which will not allow the passage of either the visible or ultraviolet rays of the sun or the rays of an electric arc light; further, that this agent is able to generate a marked fluorescence. . . . It will be found that all bodies are permeable. . . . Thick blocks of wood are also permeable. . . . Sheets of hard rubber several centimeters in thickness still permit the rays[1] to pass through. . . .

"[1]Note: For the sake of conciseness I should like to use the expression *rays,* and in order to distinguish them from others, the name X-rays."

Paroxysmal Atrial Tachycardia with Atrioventricular Block

Its Frequent Association with Chronic Pulmonary Disease

By LEONARD M. GOLDBERG, M.D., J. DAVID BRISTOW, M.D., BRENT M. PARKER, M.D., AND LEONARD W. RITZMANN, M.D.

PAROXYSMAL atrial tachycardia with atrioventricular block (PAT with block) has been recognized more often in recent years since Lown and Levine clarified its diagnostic criteria and emphasized its important relation to digitalis excess.[1, 2] The present report was prompted by the increasing frequency with which this diagnosis has been made at our hospital and its common association with chronic pulmonary disease.

Methods and Materials

The electrocardiographic files at the Portland, Oregon, Veterans Administration Hospital were reviewed for records demonstrating PAT with block. The 5-year period from January 1954 to April 1959 was covered. In those cases found, the clinical, laboratory, and autopsy data were abstracted from the hospital charts. Emphasis was placed upon the type of heart disease present, details of digitalis and diuretic therapy, treatment and course of the arrhythmia, and outcome of the basic disease process. The electrocardiograms were analyzed for details of the arrhythmia, including atrial and ventricular rates, configuration of the atrial complexes, types of A-V block, and associated rhythm disturbances.

The diagnosis of PAT with block was made solely on the basis of the electrocardiogram (fig. 1). We utilized the criteria of Lown and Levine,[1, 2] which include atrial rates of 150 to 250 per minute; varying degrees of atrioventricular block (usually 2:1, Wenckebach, or varying in type); P waves that are upright in leads II, III, and aV_F, and altered in configuration from those preceding development of the arrhythmia; an isoelectric baseline between the P waves and a P-P interval that may be slightly irregular. The degree of A-V block may be increased by carotid massage or decreased by atropine or exercise. Ventricular premature contractions may be present. Since quinidine may slow the atrial rate of atrial flutter to below 250, we did not include cases in which quinidine had been given prior to development of the arrhythmia.

From the Veterans Administration Hospital and the University of Oregon Medical School, Portland, Ore.

Results

The diagnosis of PAT with block was established in 37 cases. The patients ranged in age from 33 to 89. Although only 1 patient was female, this sex distribution is consistent with the total population of our hospital. In general, the patients were seriously ill with advanced heart disease. Thirty-four patients had organic heart disease with atherosclerotic, the most common type, present in over one third of the cases. Cor pulmonale was almost as frequent, occurring in 10 cases. In addition, there were 4 cases of hypertensive cardiovascular disease, 2 of rheumatic heart disease, and 1 case each of myocarditis, polyarteritis, congenital heart disease, and dystrophic heart disease (i.e., progressive muscular dystrophy). There were only 3 patients in whom no heart disease could be demonstrated. Two of these were digitalized because of atrial tachycardia and subsequently developed PAT with block. The heart disease was accompanied by congestive heart failure in 33 cases.

An unexpected finding was the high frequency of serious pulmonary disease (table 1); over one half of the patients had significant lung lesions. The most common was advanced obstructive emphysema, present in 10 patients; other types included pneumonia, pulmonary embolism, bronchogenic carcinoma, and tuberculosis. A total of 22 lung lesions was found in 20 patients. That the pulmonary

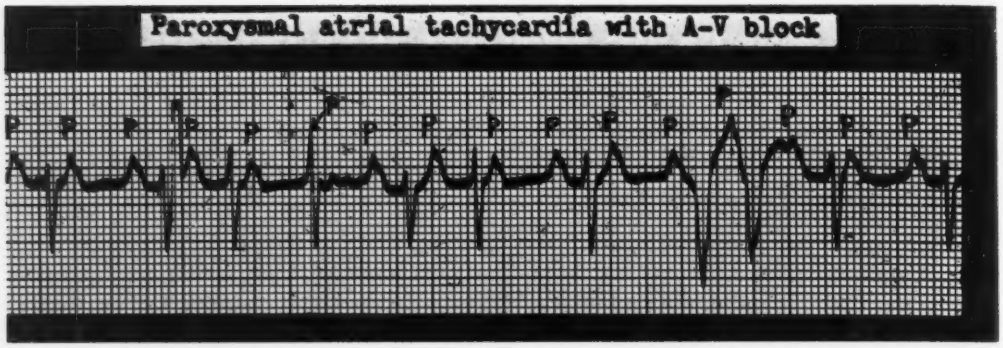

Figure 1

Characteristics of PAT with block—lead II. The atrial rate is 166. The A-V block is of Wenckebach type. The second, third, and fourth QRS complexes are preceded by P-R intervals of increasing duration. A P wave is buried in the fourth QRS; its ventricular response is blocked. The P waves are notched, peaked, and separated by isoelectric baselines. Two premature ventricular contractions are present.

process was the primary disease in many instances is attested to by the fact that definite electrocardiographic, clinical, or postmortem evidence of cor pulmonale was present in over 25 per cent of the total series. Although we have no statistical data as to the frequency of pulmonary disease in our digitalized patients, it is our impression that the occurrence of PAT with block in this group represents a higher incidence than would be expected by chance alone, since the distribution of diagnostic categories in our institution is approximately that seen in most general medical and surgical Veterans Administration Hospitals.

The basic electrocardiographic diagnosis of the series encompassed a wide variety of abnormalities. Fourteen cases had nonspecific ST-T abnormalities consistent with myocardial disease or associated digitalis effect. The second most frequent abnormality was right ventricular hypertrophy, present in 7 cases, confirming the previously mentioned high incidence of cor pulmonale. "P-pulmonale" (tall peaked P waves in leads II, III, and aV_F) was also seen to be frequent after the arrhythmia disappeared. P-pulmonale and right ventricular hypertrophy did not always coexist. The remaining electrocardiograms demonstrated left bundle-branch block, right bundle-branch block, myocardial infarction, and left ventricular hypertrophy, all in approximately equal numbers.

The PAT with block was characterized most commonly by atrial rates between 120 and 200 per minute (table 2). Two patients had atrial rates of 115 and 6 had rates between 200 and 240 (fig. 2). These cases were otherwise typical of PAT with block. In almost two thirds of the group the ventricular rate was less than 100, and in only 1 instance was it above 150 per minute. All types of A-V block, from first degree to complete, were recorded, and in many cases there was a shift from one type to another. The predominant type of A-V block was 2:1 (15 cases); changing block and Wenckebach phenomenon were present in almost equal numbers. As a consequence of the relatively slow ventricular rate and the occasionally regular ventricular rhythm (2:1 block) an arrhythmia was frequently unsuspected at the bedside. Indeed, it was often discovered in an electrocardiogram obtained for other purposes. When the rate was more rapid and the block changing, atrial fibrillation was occasionally simulated.

PAT with block was the sole rhythm disturbance in only 6 instances. Premature ventricular contractions, often a sign of digitalis excess, occurred concomitantly in 18 cases. A variety of other arrhythmias, predominantly

Table 1

Types of Pulmonary Disease

Obstructive emphysema	10
Pneumonia	3
Pulmonary embolism	2
Bronchogenic carcinoma	2
Tuberculosis	2
Fibrothorax*	1
Polyarteritis	1
Granulomatosis	1

*Chronic tuberculous pleuritis with absent expansion of the right hemithorax.

supraventricular, either preceded or followed the PAT with block. Some of these, such as A-V dissociation and A-V nodal rhythm, also were thought to corroborate the suspicion of digitalis intoxication.

At the time of development of PAT with block all but 1 of the patients were receiving digitalis. Although it was often difficult to establish the presence of digitalis toxicity, especially in retrospect, review of the records revealed that in 22 patients there were clinical reasons in addition to the arrhythmia to suspect digitalis toxicity. It was of interest that all types of digitalis preparations were represented in the group. In 22 cases diuretics had also been administered shortly before the arrhythmia appeared. Nevertheless, the serum potassium was reduced (less than 3.5 mEq. per liter) in only 4 of the 23 patients in whom it was measured prior to potassium therapy.

PAT with block was managed by stopping digitalis or by administering potassium salts in 31 cases. Nine patients received procaine amide or quinidine in addition. Of this total of 31, only 3 died with the arrhythmia persisting. In the remaining 6 patients the rhythm disorder was not recognized and therefore not treated, and 4 of this group died with it still present. Despite the fact that only 7 patients died without conversion of the arrhythmia, 18 were dead within 1 month after development of the PAT with block, and a total of 22 died within 1 year. These figures point out the seriousness of the underlying heart disease with which PAT with block is usually associated.

Table 2

Electrocardiographic Characteristics of Thirty-seven Cases of PAT with Block

Rate per minute	Less than 100	100-120	121-150	151-200	More than 200
Atrial	—	2	10	19	6
Ventricular	23	5	8	1	—

Type of A-V block	
2:1	15
Varying	11
Wenckebach	9
Complete	2

Discussion

The principal arrhythmias with which PAT with block may be confused are atrial flutter, atrial tachycardia, and sinus tachycardia. The absence of a constantly undulating baseline, the presence of upright P waves in leads II, III, and aV_F, and an atrial rate less than 250 are features that help to distinguish PAT with block from atrial flutter. Occasionally there may be confusion when the atrial rate in flutter is slowed by quinidine therapy. In this instance, however, the previous records and the clinical history will be of diagnostic importance. Careful examination of the electrocardiograms will reveal the evidences of A-V block that separate the disorder under discussion from paroxysmal atrial tachycardia or sinus tachycardia. A changed configuration of the P waves will also help to differentiate this entity from sinus tachycardia with A-V block.

Although the atrial rate in PAT with block is ordinarily said to be 150 to 250,[1, 3] 12 of our cases had rates less than 150 per minute. In 2 of these the rate was 115 per minute, but all the other criteria for the diagnosis were met. Indeed, Lown et al.[3] in their recent series of 23 cases listed 9 in which the atrial rates were less than 150, with one as low as 100. Thus, we think that the usually stated range should be broadened to encompass slower atrial rates.

Since the ventricular rates in our cases were rarely greater than 120 and generally less than 100 per minute, it seems unlikely that the arrhythmia itself was directly detri-

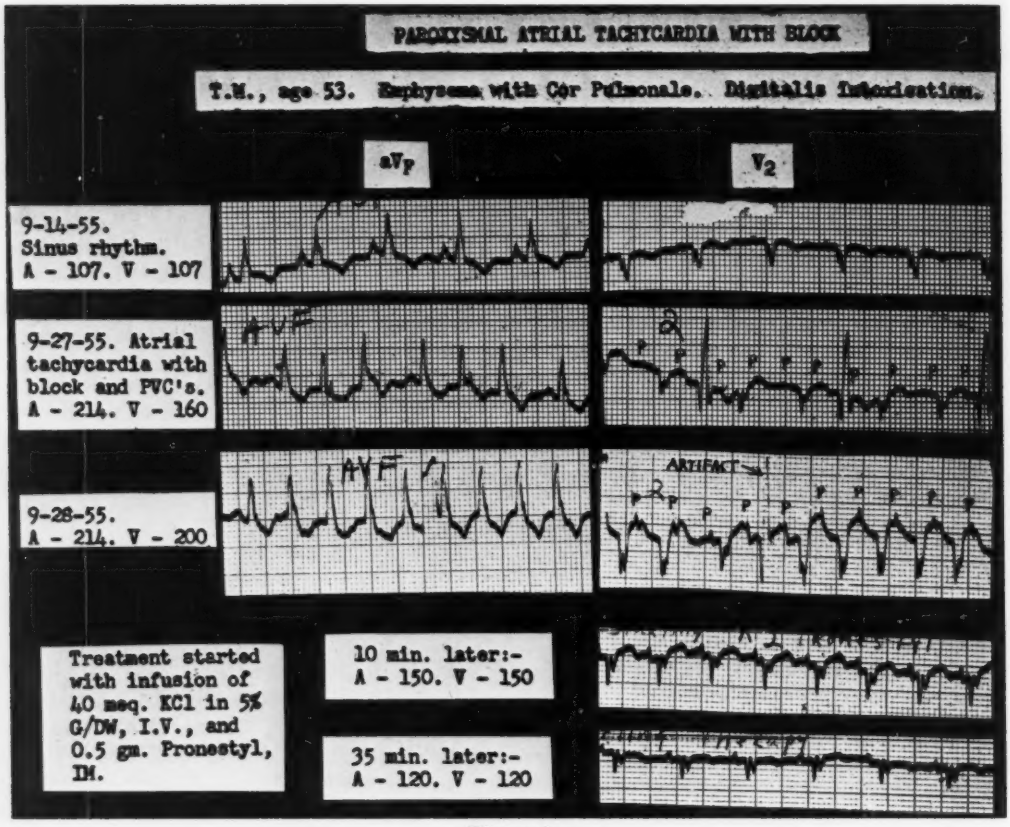

Figure 2

PAT with block displaying rapid atrial and ventricular rates in a patient with cor pulmonale. PAT with Wenckebach type of A-V block developed on 9/27/55 and was present the following day with a more rapid ventricular rate. Lead V_2 best shows the P waves. Sinus rhythm was restored 10 minutes after procaine amide and potassium therapy was begun.

mental to cardiac function and blood flow. Its importance, rather, was that it denoted potentially dangerous digitalis toxicity. Because PAT with block accompanied serious heart disease, the prognosis for the patients in whom it occurred was usually, though not always, grave.

The association of PAT with block and digitalis toxicity has been clearly elucidated, as has the response to potassium therapy.[1-11] Our results are confirmatory in both respects (fig. 3). There was evidence of digitalis toxicity in almost two thirds of the patients, and the arrhythmia ceased after withdrawal of digitalis and administration of potassium in 28 of 31 patients. A low serum potassium was not demonstrated in most of our patients despite prior diuretic therapy. It is known, however, that in nearly all chronic diseases, including congestive heart failure, the total body exchangeable potassium is low,[15] a state well known to potentiate rhythm disorders by increasing the effect of digitalis.[5, 16]

Although digitalis toxicity is usually incriminated as a mechanism in the genesis of this arrhythmia, a number of cases have been reported in which digitalis was not being given at the time this rhythm disturbance

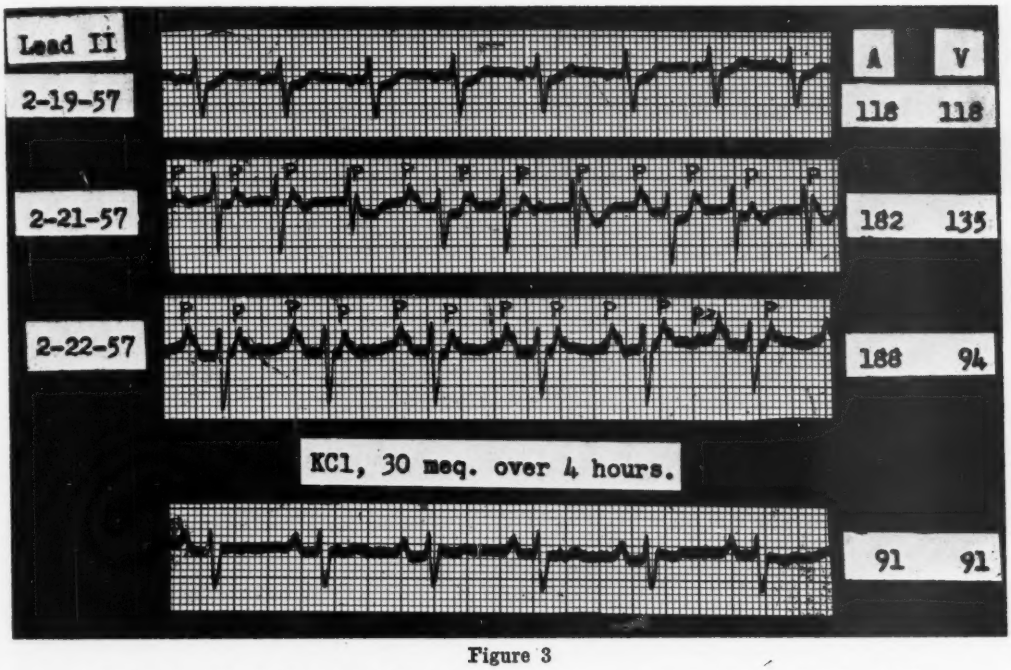

Figure 3

Typical example of PAT with block from a patient with cor pulmonale. The first strip shows lower atrial tachycardia with a rate of 118. Two days later, after vigorous digitalis and diuretic therapy, PAT with Wenckebach phenomenon was present; succeeded the following day by persistent 2:1 A-V block. Potassium therapy restored sinus rhythm within 4 hours.

occurred.[13, 17] At least 2 of our cases fit this category.

One of the most interesting features of our group was the association of PAT with block and serious pulmonary disease. As stated previously, there were 20 patients in whom the conditions coexisted and 10 in whom the major cardiologic diagnosis was cor pulmonale. An association of PAT with block and chronic lung disease has not been described heretofore. Although some authors have expressed the opinion that arrhythmias are infrequent in the presence of cor pulmonale,[12, 18, 19] our view is to the contrary. Recent studies tend to confirm this impression. Corazza and Pastor[20] reported that 31 per cent of 122 patients with pulmonary heart disease had arrhythmias. It is known that acidosis, anoxia, pulmonary hypertension, and distention of the right atrium and great veins, any or all of which may exist in the presence of serious pulmonary heart disease, may be associated with increased atrial irritability and stimulation of ectopic pacemakers. In addition, patients with cor pulmonale tend to respond poorly to medical measures, so that digitalis may be given in larger than usual amounts in an attempt to improve right heart failure. Baum et al.[22] have reported that of 29 patients with pulmonary insufficiency, 8 exhibited evidences of digitalis toxicity that they attributed to anoxia. Whatever the cause, we think that one should be especially assiduous in watching for PAT with block in digitalized patients with cor pulmonale.

Summary

Paroxysmal atrial tachycardia with block is a cardiac arrhythmia that is usually a manifestation of digitalis toxicity in patients with

serious heart disease. The arrhythmia generally ends promptly after potassium administration and withdrawal of digitalis. Since the ventricular rates may be slow and regular, the arrhythmia may be difficult to recognize clinically. Atrial rates as slow as 115 per minute may be seen in cases which are otherwise typical of the condition.

In our series associated pulmonary disease was present in 54 per cent and cor pulmonale in 27 per cent of the cases.

Summario in Interlingua

Paroxysmic tachycardia atrial con bloco es un arrhythmia cardiac que usualmente representa un manifestation de toxicitate per digitalis in patientes con serie morbo cardiac. Iste arrhythmia se termina promptemente in le majoritate del casos post le administration de kalium e le suppression de digitalis. Proque le frequentia ventricular pote esser lente e regular, il occurre que iste arrhythmia es difficile a recognoscer clinicamente. Frequentias atrial de non plus que 115 per minuta ha essite observate in casos que es alteremente typic del condition.

In nostre serie, associate morbo pulmonar esseva presente in 54 pro cento e corde pulmonal in 27 pro cento del casos.

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Serum Potassium and the Electrocardiogram in Hypokalemia

By WALT F. WEAVER, M.D., AND HOWARD B. BURCHELL, M.D.

THE purpose of this study is to correlate changes observed in the electrocardiogram with varying concentrations of serum potassium in commonly encountered clinical conditions.

There has been much discussion and some disagreement in the literature concerning electrocardiographic criteria for hypokalemia. Many studies have dealt with the combination of 2 decidedly different aspects of hypokalemic states, namely the acute and the chronic. The electrocardiographic change may be related to the myocardial intracellular potassium, the myocardial extracellular potassium, the serum potassium, the transmembranous gradient of potassium, the rate of transmembranous diffusion of potassium, or the transmembranous gradient of hydrogen ion. It is not the purpose of this paper to present the merits or details of these various theories. Many of these phenomena would necessarily be affected by other factors such as the concentration of other electrolytes and the environmental pH. Until more is known of the physiologic and biochemical mechanisms of body potassium and their relationship to total acid-base and electrolyte balance it may be difficult to use patients with acute transient hypokalemia who have a rapid alteration of their internal and external environment for the enunciation of electrocardiographic criteria for hypokalemia.

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Based, in part, on the thesis submitted by Dr. Weaver to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Although of interest in cases of suspected or proved electrolyte imbalance, the electrocardiogram is often valuable in those clinical conditions in which hypokalemia often is not clinically apparent. Such states would include primary aldosteronism,[1] familial periodic paralysis, chronic diarrhea, gastroileal anastomoses, potassium-losing nephritis, and hypokalemia secondary to diuretic therapy. The electrocardiogram is useful also when facilities for potassium determinations are not readily accessible or estimation of serum potassium is needed immediately.

Materials and Methods

A study was made of 1,800 patients who had concentrations of serum potassium of less than 4.0 mEq. per liter. Of these 1,800 patients, 850 had had an electrocardiogram recorded near the time that blood was withdrawn for determination of potassium. In an attempt to minimize the number of variables in the study, the following types of cases were discarded from the study: (1) those in which unsteady clinical states, such as diabetic acidosis, hemodialysis, and postoperative periods were indicated; (2) those in which the electrocardiogram showed evidence of myocardial ischemia, ventricular rates in excess of 100, ventricular conduction defects, or rhythm disturbances; and (3) those of patients treated with digitalis or quinidine. Thus 130 patients who had one or more values for serum potassium of less than 4.0 mEq. were selected. Several patients had serial determinations and in 152 instances the serum potassium was determined with nearly simultaneous recording of the electrocardiogram.

Other serum electrolytes also were determined in the majority of instances. Various observations were made on the electrocardiogram including rate, P-R interval, Q-T interval, amplitude of QRS complexes, deviations of S-T segment, amplitudes of T and U waves, and the incidence of ventricular and atrial premature contractions. Other abnormalities, such as left ventricular hyper-

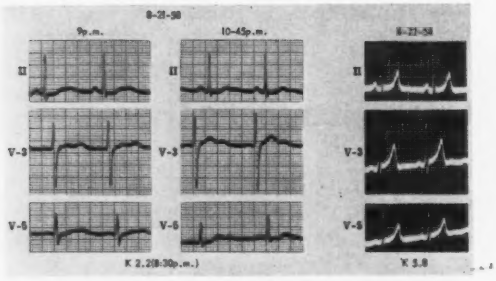

Figure 1

Effect of intravenous administration of potassium. The tracing made at 9 p.m. shows the classic hypokalemic pattern with S-T depression, partial fusion of T and U waves, with U being of abnormal amplitude (2 mm.) and taller than T (T/U less than 1). Administration of potassium resulted in elevation of S-T segment, elevation of T waves, and lowering of U waves with restoration of normal T/U relationship. U is still abnormally tall but a later tracing (hyperkalemia) shows normal U waves as well as peaked T waves and elevation of the S-T segment. Lead V_3 of the tracing made at 10:45 p.m. shows that the measured Q-T interval (onset of QRS complex to T-U notch) would be shorter than the true Q-T interval, since the T wave is not isoelectric at this point. If the T wave slope were extrapolated, the true Q-T interval might be 0.04 to 0.06 second longer.

trophy, were also noted. The ratio of serum sodium to potassium was calculated in all instances in which the value for serum sodium was available. The Q-T index was calculated by means of the Bazett formula $\left(\text{Q-T index} = \sqrt{\frac{\text{Q-T observed}}{\text{R-R interval}}}\right)$. The normal Q-T index with this formula is 35 to 44. The ratios of the T-wave amplitude to the U-wave amplitude and of the T-wave to the R-wave amplitude were calculated in all cases in leads II and V_3. The presence or absence of hypertension was noted, and the patients were divided into 3 groups —hypertensive patients alone, normotensive patients alone, and all patients. Each of the 3 groups was then subdivided on the basis of serum potassium concentration into 4 smaller groups.

Additional Electrocardiographic Observations

The Q-T interval was measured in all but 5 instances (in which there was fusion of T-U complexes).[2] In several instances it was necessary to measure the Q-T interval from the onset of the QRS complex to the notch between the T and U waves as suggested by Lepeschkin and Surawicz.[3] This maneuver would of course tend to make the measured Q-T interval shorter than the true Q-T interval (fig. 1). Q-T values corrected for rate and sex were obtained from Lepeschkin's data.[4] As a means of comparison, other normal values from Koch[5] and Bazett's formula[6] also were used.

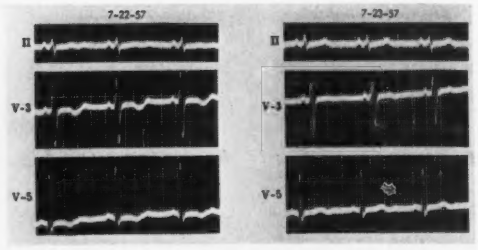

Figure 2

The value for serum potassium was 3.4 mEq. on 7-22-57 and 3.8 mEq. on 7-23-57. The inverted T waves in leads V_3 and V_5 became upright with elevation of serum potassium. Also the prominent U waves on 7-22-57 became barely perceptible on 7-23-57.

Measurement of amplitudes of T and U waves was frequently difficult due to lack of isoelectric (base-line) periods in the electrocardiogram. When this occurred the Pt_A segment was used as a reference point.

Two sets of T/R values were calculated: one from the precordial lead where the highest T wave was commonly found (usually lead V_3 and the other from the left ventricular complexes which gave the largest T/R values as suggested by Reynolds and associates.[7]

Results

Approximately half of the patients in the study were clinically hypertensive even though the initial selection was on the basis of a low concentration of serum potassium. After careful review of the records, it was noted that in all instances the abnormalities consistent with hypokalemia could be observed in standard lead II and precordial lead V_3.

Q-T Abnormalities

There is good evidence that the Q-T index is at the upper limits of normal (table 1). As

Table 1

Electrocardiographic Measurements at Varied Serum Potassium Concentrations

Patients	Concentration of potassium in serum (mEq. per L.)	Determinations, number	Mean values							
			Q-T index		T wave (mm.)		U wave (mm.)		Deviation of S-T segment (mm.), Lead II	P-R interval (sec.)
			Mean	S.D.*	Lead II	Lead V_3	Lead II	Lead V_3		
All	<2.6	16	40.8	5.21	0.6	1.1	1.5	2.0	—0.5	0.18
	2.6-3.0	26	44.8	4.38	1.1	3.3	0.6	1.3	—0.06	0.18
	3.1-3.5	65	43.6	3.11	1.2	2.8	0.3	0.7	—0.06	0.17
	>3.5	45	42.5	2.91	1.3	3.5	0.2	0.5	—0.09	0.17
Hypertensive	<3.0	15	46.8	2.66	0.7	2.9	0.6	1.8	—0.4	0.17
	3.0-3.3	19	44.6	3.65	1.0	3.2	0.3	0.9	0	0.16
	3.4-3.6	25	43.6	2.67	0.8	4.4	0.3	0.8	—0.1	0.17
	>3.6	19	42.8	3.65	1.3	2.8	0.2	0.6	—0.1	0.17
Normotensive	<2.6	12	38.7	4.74	0.6	1.5	1.6	1.9	—0.4	0.19
	2.6-3.0	14	43.3	4.70	1.5	2.8	0.8	1.2	0.04	0.18
	3.1-3.5	29	42.7	2.54	1.5	2.1	0.3	0.6	—0.03	0.17
	>3.5	19	42.0	2.61	1.7	3.1	0.2	0.3	—0.1	0.17

*Standard deviation.

has been noted, the Q-T index contains a rate-correction factor. If observed Q-T intervals are to be compared to other normals it is readily seen that they must be evaluated individually or expressed as normal, greater than normal, or less than normal, as seen in table 2.

T-Wave Changes

The voltage of the T waves in leads II and V_3 varied as shown in table 1. Inverted T waves were present in lead II in 13 per cent and in lead V_3 in 11 per cent of our patients having hypokalemia (potassium less than 3.6 mEq.) (table 3). There was a paucity of chronically hypokalemic patients who had serial electrocardiograms with simultaneous determinations for serum potassium. However, in 2 cases an upright T wave became inverted as the concentration of potassium decreased, and in 3 cases an inverted T wave became upright as the concentration of potassium decreased (figs. 2, 3, and 4). The latter phenomenon also may occur as a result of fusion of the U wave with the inverted T wave (fig. 4).

U-Wave Changes

U waves were noted in 90 per cent of the electrocardiograms in this study. U-wave voltage in leads II and V_3 increased as the concentration of serum potassium decreased (table 1; fig. 1).

T-U fusion of all degrees occurred with hypokalemia (figs. 1, and 3 to 6). Some authors[3] have devised methods for differentiating notched T waves from T-U fusion by means of comparisons between "Q_aT and Q_aU intervals." These measurements were performed in all cases in which they were applicable, but we found that this is not an infallible method of differentiating a T wave from a U wave. Both the intravenous administration of calcium and the simultaneous recording of heart sounds are especially helpful technics in delineating U waves but they are not available in retrospective studies such as this.

Relationship of T and U Waves

More important than the actual amplitude of the U wave is the relationship between the amplitudes of T and U waves. When the T/U

Table 2

Comparison of Methods Used to Determine Q-T Abnormality: Concentration of Serum Potassium, < 3.0 mEq. (38 Patients)

Values* used for comparison	Per cent of patients		
	Q-T <normal	Q-T normal	Q-T >normal
Bazett's†	3	44	53
Koch's[5]	3	55	42
Lepeschkin's[4]	16	60	24

*The "normal" Q-T values stated by these authors were used for comparison.

†Bazett's formula, quoted in Winsor.[6]

Table 3

Incidence of Inverted T Waves in Hypokalemic Patients: Concentration of Serum Potasium, < 3.6 mEq.

Patients	Per cent	
	Lead II	Lead V_3
Normotensive (56)	11	14
Hypertensive (51)	16	8
All	13	11

Table 4

Incidence of Extrasystoles

Premature contractions	Control (ambulant patients, per cent) of 1,061 cases	Hypokalemic patients (value for potassium, <3.6 mEq; no drugs)	
		Normotensive, per cent of 51 cases	Hypertensive, per cent of 51 cases
Ventricular only	8	8	8
Atrial only	4	8	18
Ventricular and atrial	1	8	4
Total	13	24	30

value is 0.5 or less, hypokalemia usually has developed (fig. 7). When T waves are negative, the T/U value becomes negative, but even when these values are plotted they help to reinforce the contour of the initial portion of the curve; that is, a negative T/U value usually indicates an exceedingly low concentration of potassium in the serum.

S-T Segment

Depression of the S-T segment in lead II is a frequent finding in patients with a value for serum potassium of less than 2.6 mEq. (table 1). Isoelectric or depressed S-T segments in lead V_1 to lead V_3 were noted in several hypokalemic patients who had electrocardiographic evidence of left ventricular hypertrophy or left ventricular strain.

P-R Interval

P-R intervals remained in normal ranges for all groups (table 1). The P-R interval was consistently higher with hypokalemia, but this finding was not statistically significant. In isolated cases in which serial electrocardiograms were made the P-R interval was noted to increase slightly with decreased concentration of serum potassium.

P Waves

The P waves were not measured, but in several cases in which serial electrocardiograms were made the P-wave voltage was noted to increase slightly as the potassium decreased (fig. 3).

T-R Relationship

Our use of the method of Reynolds and associates[7] showed only a minimal degree of correlation in the normotensive patients between the serum potassium and the T/R values. There was no correlation in the group of hypertensive patients.

Premature Contractions

A significant increase developed in atrial premature contractions as shown in table 4.

Ratio of Sodium to Potassium

The ratio of serum sodium to potassium showed an almost straight-line relationship to the concentration of serum potassium (fig. 8).

Index Hypertension

The influence of hypertension on the QT_C in hypokalemia is shown in table 1. It has long been known that the Q-T interval is increased in the presence of hypertension.[8-10] The T waves differed in the hypertensive group as would be expected, that is, they were lower in lead II and higher in lead V_3 (table 1). Hypertension apparently did not affect amplitude of U waves, deviations of S-T segment, or P-R intervals (table 1).

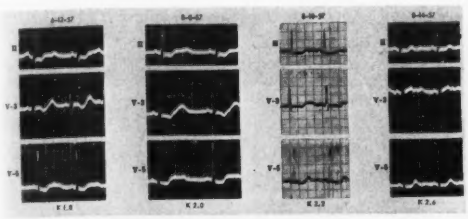

Figure 3

The amplitude of the P wave was increased in lead II of patient with hypokalemia. There was progressive change of inverted T wave to upright T wave in lead II with increasing concentration of potassium. The U wave lowered progressively and the S-T segment returned toward normal. In leads V_3 and V_5 the T-wave inversion decreased progressively with a final upright T wave as potassium repletion occurred. The apparent increase of U-wave amplitude is due to gradual shift upward of the terminal portion of the T wave which is the U-wave take-off point. The actual amplitude of the U wave decreases with the increasing concentration of potassium. A third diastolic potential is present in lead V_3 in tracing dated 8-14-57. This may be a notched T wave, notched U wave, or positive after-potential.

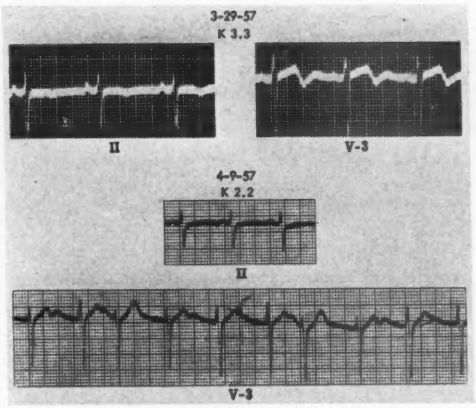

Figure 4

Note the change in contour and amplitude of the P wave in lead II. The S-T depression is seen in leads II and V_3 with hypokalemia. An inverted T wave in lead II and a diphasic T wave in lead V_3 become upright with hypokalemia. Note increased numbers of atrial premature contractions. Note also the influence of these contractions on early ventricular diastolic filling pressure and hence the influence on the U wave. In this record it appears that during diastole the effect is greater on the position of the U wave (Q-U interval) than on its amplitude. It is also possible that the changes in the U wave (which repeat every 3 cycles) cause the atrial premature contractions. The terminal inverted portion of the T wave is seen to be pulled up by the appearance of a higher U wave.

Acid-Base Abnormalities

There were 5 severely hypokalemic patients (potassium 2.9 mEq. or less) whose electrocardiograms were not typical of hypokalemia insofar as our established criteria for hypokalemia. In these patients the acid-base balance was disturbed, manifested either by low carbon dioxide combining power or low serum concentration of sodium (fig. 9). Another patient had an electrocardiogram that was typical of hypokalemia yet the value for serum potassium was 3.2 mEq. However, the value for carbon dioxide was 42.5 mEq. in this patient (fig. 5).

Discussion

Sidney Ringer[11, 12] in 1883 first emphasized the importance of potassium and other ions in maintenance of normal cardiac function. There are numerous reports[13–23] of myocardial degeneration and of fibrosis as a result of potassium depletion. Whether the disturbed cellular function is dependent on relative (myocardial only) or absolute (total body) depletion of potassium is not clear. Other factors undoubtedly are involved. Similarly the electric manifestations of cellular function are disturbed with variations in the concentration of potassium.

Some investigators[24, 25] have stated that the electrocardiogram cannot be relied on as a guide to potassium depletion. Others[7, 26–28] have stated certain levels below which the electrocardiogram is a reliable guide. As has been implied, many factors determine the reliability of the electrocardiogram as an indicator of hypokalemia. Using dogs that were rendered acutely hypokalemic by dialysis, Nichopoulos and Hoffman[29] found depression of the S-T segment and depression or inversion of the T waves to be the most consistent findings in the electrocardiogram. They did not note changes in the P-R interval and P waves, and U waves did not appear. Interestingly, they found an increase of 12 per cent

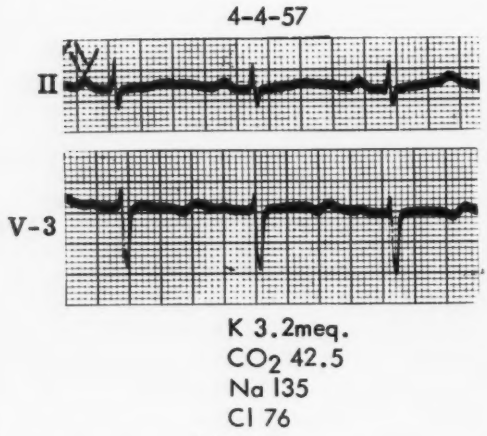

Figure 5

Note slurred prolonged T-U fusion pattern in lead II. Note also the inverted T wave and upright U wave in lead V_3. The electrocardiogram suggests more hypopotassemia than is actually present. Perhaps an alkalotic state contributed to abnormal pattern.

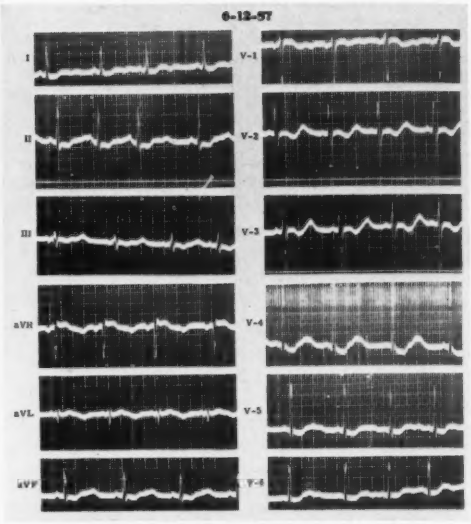

Figure 6

The value for serum potassium was 1.8 mEq. Note numerous atrial premature contractions. There are bizarre undulating diastolic potentials representing fusion of T waves, U waves, and possibly positive after-potentials. In some leads, separate waves are seen, yet in lead V_3 the T-U fusion pattern might often be mislabeled as a diphasic T wave. The difficulty of Q-T measurement in such a tracing is obvious.

in myocardial potassium in hypokalemic dogs over that of dogs in the control group.

Weller and associates[30] used dialysis to remove potassium from dogs and noted the first effect to be an increase in the height and width of the P wave. They noted increased A-V conduction time and eventually the P waves migrated and fused with the T and U waves. They also noted depression of the S-T segment which persisted for several hours after the serum potassium returned to normal levels. Bellet and co-workers[31] described different electrocardiographic changes for various etiologic types of hypokalemia. The foregoing remarks serve to introduce the complexities involved in evaluation of the electrocardiographic signs of hypokalemia.

Q-T Interval

The relationship of Q-T interval to concentration of serum potassium has been studied frequently by many investigators. Originally the Q-T interval was thought to be prolonged by hypokalemia.[7, 32-34] Ernstene and Proudfit[35] were the first to suggest that fusion of U waves with T waves causes an apparent lengthening of the Q-T interval. Some authors[3, 26, 36] have suggested that the Q-T interval is actually normal or short. Another source of difficulty arises from not knowing the normal Q-T value and the effect of heart rate, blood pressure, sex, and other variables on it. The measurement of the Q-T interval is subject to some error. There may be isoelectric periods at both ends (QRS and T) of the interval in various leads.

Furbetta and co-workers[37] pointed out the relatively large errors encountered even when simultaneous recording of heart tones is performed. Klakeg and associates[38] emphasized that the Q-T interval may not be of the same duration as mechanical systole, particularly at slower rates. As previously stated, occasionally the measured Q-T interval (when minimal T-U fusion is present) will tend to be shorter than the true Q-T interval so that normal or prolonged Q-T intervals in our

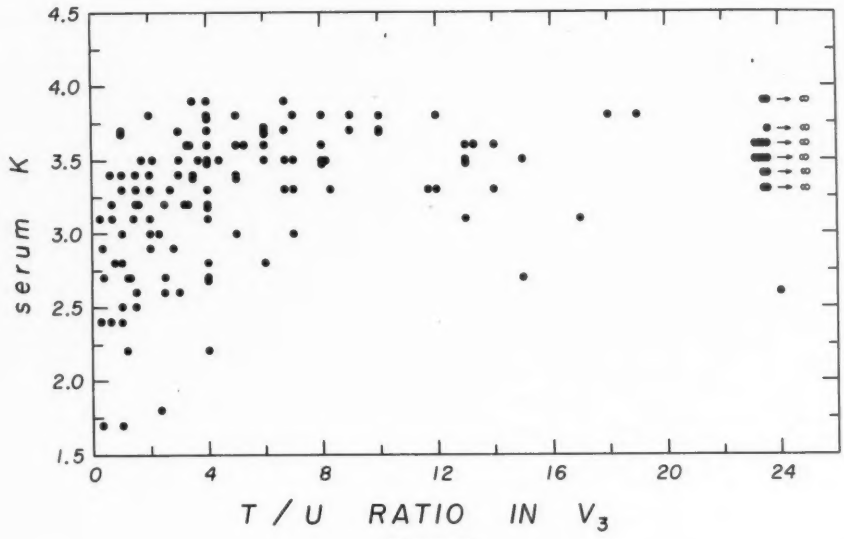

Figure 7

Relationship between T/U values in precordial lead V_3 and the serum potassium concentration.

study are even more meaningful. The use of available normal limits, however, makes it justifiable to conclude that the Q-T interval may be slightly prolonged in hypokalemia; the Q-T interval is either at or above the upper limits of normal in most cases (table 1).

T Waves

Inversion of the T waves has long been considered an electrocardiographic sign of hypokalemia.[27, 29, 31, 36, 39–41] In the literature, the difference between the phrases "inverted T waves" and "inversion of the T waves" must be noted carefully. Inversion of T waves is by definition a phenomenon that requires more than one electrocardiogram for its recognition. We have mentioned that inverted T waves were present in some cases in this study (table 3) (figs. 2 to 6). It is obvious that the presence of an inverted T wave in a single electrocardiogram is not nearly so important as an inverted T wave that was upright in previous electrocardiograms. Although hyperkalemia has been shown to increase the amplitude of an inverted T wave,[42] data are insufficient to give statistical support to the opposite phenomenon with hypokalemia, that is, a decrease in amplitude of an inverted T wave. The effect of potassium also may vary depending on the initial cause of the T-wave inversion.[42–44] When dealing with the problems of T-wave inversion one must be certain to observe the T wave and not the T-U complex (fig. 3).

Another interesting T-wave phenomenon that we observed was a decrease in the slope of the descending limb of the T wave with hypokalemia. This is partly a function of loss of T-wave amplitude, but in figure 1 the so-called normal T wave has an opposite shape; the descending limb is steeper than the ascending limb. This decrease in slope occurred in cases with separate distinct U waves. It is probably what some authors[35–47] refer to as a positive after-potential, which is usually seen as broad T-wave notching or slurring of the descending portion of the T-wave. Although the positive after-potential occurs commonly during hypokalemia according to Sjöstrand,[39] changes in the U waves seem to be found more consistently in this study. Indeed we are of the opinion that in some cases of severe hypokalemia the bizarre undulations observed during repolarization are combinations of T waves,

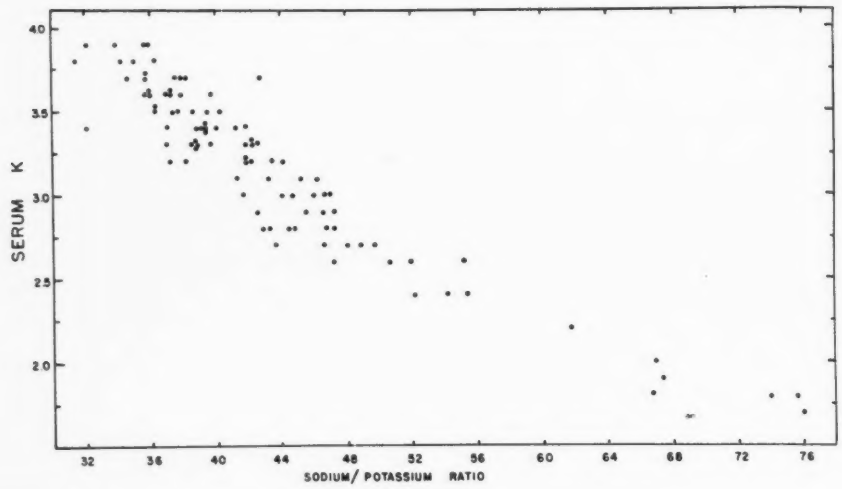

Figure 8

Relationship between the serum sodium-potassium ratio and the serum potassium concentration.

positive after-potentials, and U waves (figs. 3 and 6).

U Waves

The 4 main theories concerning the etiology of U waves are as follows: (1) caused by after-potentials which follow the action-potential proper, (2) caused by potentials elicited by the stretching of ventricular muscle during the stage of rapid filling, (3) caused by longer duration of action-potentials in some sections of the ventricles, and (4) caused by repolarization of the papillary muscles and interconnected structures.

Furbetta and associates[48] are proponents of the last-named theory and refer to abnormalities of the U wave and T-U segment as the "papillary muscle syndrome." Lepeschkin[4] has favored the first theory and it seems the best available theory with good supportive experimental evidence. Certainly the factors mentioned in the other theories play some role in U-wave genesis.

Cannon and Sjöstrand[46] suggested the presence of 2 separate diastolic potentials in the electrocardiogram — the positive after-potential and the U wave. Their positive after-potential is an electrocardiographic phenomenon and is not synonymous with the after-potentials of a monophasic action-potential. They described the positive after-potential as a slowly subsiding positive potential following the mechanical systole and appearing at the conclusion of the refractory period and T wave. They stated that hypokalemia causes appearance of the positive after-potential. Sjöstrand[39] later stated that whereas the positive after-potential varies inversely with the concentration of serum potassium, "the U wave varied apparently irrespective of the potassium concentration in the serum."

In a study of 100 electrocardiograms of normal patients Furbetta and associates[49] found U waves in 99 per cent of electrocardiograms in lead V_3 and 92 per cent in lead II. Electrocardiograms in 23 per cent of their cases showed U-wave amplitudes greater than 1 mm. and in 2 the U-wave amplitudes were greater than 2 mm. Lepeschkin[4] stated that the U wave is seen in nearly 100 per cent of cases but noted amplitudes greater than 1 mm. in only 2 per cent of cases.

In addition to hypokalemia and related disturbances, U waves can be unusually high due to bradycardia, epinephrine, thyrotoxicosis, exercise, increased QRS amplitude, left ventricular hypertrophy, hypertension, and the therapeutic combination of digitalis and

quinidine.[4, 36, 50] Changes in potassium may change the amplitude *and polarity* of T waves but only the amplitude of U waves.[51]

Thompson[52] in 1939 and Tarail[32] in 1948 published the first articles dealing specifically with the relationship of the electrocardiogram to serum potassium concentration. Although not specifically mentioned, U waves were present in the published electrocardiograms. Also in 1948 Nadler and co-workers[53] implied a relationship between U waves and the concentration of serum potassium. They noted the appearance of U waves when the potassium was low during treatment of diabetic acidosis and their disappearance when potassium was administered to the patient. There have been numerous isolated reports of electrocardiograms taken when a low concentration of serum potassium was known or suspected.

Stewart and associates[54] referred to a case of familial periodic paralysis reported by Janota and Weber[55] and noted, in a case of their own, prolongation of the P-R interval, the QRS interval, and the Q-T interval and a decrease in amplitude of T waves. U waves were present in their published records but were not recognized as such.

In 1944, Brown and associates[56] reported cases of 3 patients who had muscular paralysis and electrocardiographic abnormalities with low concentrations of potassium. They noted the appearance of U waves but did not see any relationship to the low values for serum potassium. They said, "The prominence of the U waves is of interest but the explanation of this remains obscure."

These and other reports[33, 57-59] point out changes in T waves and other changes with known low concentrations of serum potassium or conditions commonly associated with hypokalemia, and most of them show records with prominent U waves. Yet the relationship of the U wave to the concentration of serum potassium was not suggested until 1948.[53] Since 1948 many investigators have noted and studied this relationship.

Bellet and co-workers[31] in 1950 found U waves in 42 per cent of the electrocardiograms

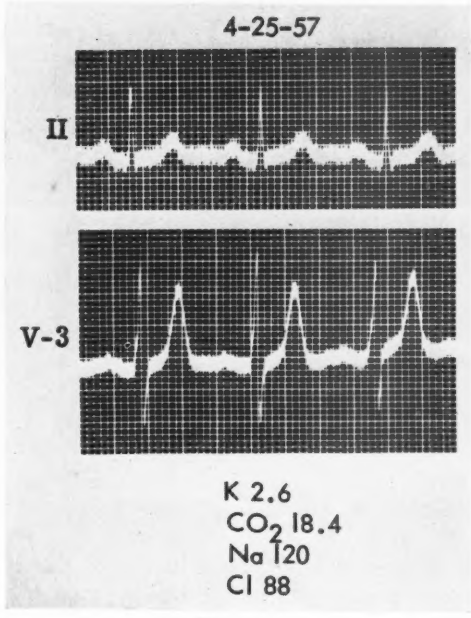

Figure 9

Effect of acidosis on hypokalemic pattern. Note tall T waves and unusually low (lead II) U waves.

of patients with hypokalemia. Reynolds and associates[7] in 1951 noted that 55 per cent of all patients with concentrations of serum potassium of less than 4.0 mEq. had U waves. Of their patients with a value for serum potassium of less than 3.0 mEq., 35 per cent had "large" U waves. Surawicz and Lepeschkin[36] in 1953 noted an increase in amplitude of the precordial U waves with hypokalemia and also commented on T-U fusion and ways of differentiating the Q-T interval from the Q-U interval. Schwartz and co-workers[25] first suggested the importance of the relationship of U-wave amplitude to T-wave amplitude. However, they concluded that "in potassium depletion of moderate severity the electrocardiogram cannot be relied upon as a guide to diagnosis or treatment." Lepeschkin[4, 60] in 1955 suggested possible electrophysiologic explanations for the formation of the U wave in its relationship to the concentration of serum potassium. Bellet[27] in 1955 commented on the increased amplitude of U waves with hypo-

Table 5

Electrocardiographic Criteria for Hypokalemia

Electrocardiographic signs	Value*
T/U 1 or less in lead II	1
T/U 1 or less in lead V_3	1
U_{II} 0.6-1.4 mm.	1
U_{II} 1.5 or greater	2
U_{V_3} 1.1-1.9 mm.	1
U_{V_3} 2.0 or greater	2
S-T Depression of 0.5 mm. or greater in lead II or leads V_1 to V_3	1

*Electrocardiographic score:
0-1, nondiagnostic
2, suggestive
3-7, characteristic

kalemia and noted T-U and U-P fusion patterns. Surawicz and co-workers[26] in 1957 related actual measured amplitudes of the U waves to varying levels of serum potassium. They also utilized the U/T amplitude relationship and correlated several electrocardiographic "signs" with serum potassium levels.

Relationship of T and R Waves

The relationship of T and R waves has not been studied extensively but Reynolds and associates[7] found that the T-wave amplitude was consistently less than 15 per cent of the R-wave amplitude when the concentration of serum potassium was less than 3.0 mEq. We were not able to find a good correlation between the serum potassium concentration and the amplitudes of T and R waves in lead II, lead V_3, or the precordial leads showing a left ventricular type of complex as suggested by Reynolds.

Atrial Abnormalities

The abnormalities occasionally associated with hypokalemia are increased amplitude of the P waves and increased P-R interval.[30, 54, 61] The problem of atrial premature contractions will be discussed subsequently. There is a slight but statistically insignificant increase in P-R intervals in our study. Most of the few available serial electrocardiograms show an increased P-wave amplitude with hypokalemia (figs. 3 and 4). It should also be remembered that U-P fusion as well as T-U fusion can occur and the U-P fusion has occasionally been misinterpreted as P-wave increase and distortion with hypokalemia.

The appearance of atrial premature contractions with hypokalemia (figs. 4 and 6) has been commented on before in isolated cases.[27, 34] However, to our knowledge no incidence for a series of cases has been reported. The mechanism of production of ventricular premature beats and their relationship to U waves has been extensively discussed recently.[62] The effect of potassium on conduction and ectopic rhythms also has been discussed recently.[63] The U wave of the electrocardiogram corresponds to a supernormal phase of excitability and one notes that U-wave amplitude increases as the level of excitability increases, the effect of quinidine being an exception. It is difficult to ascertain which phenomenon comes first, that is, tall U waves or increased excitability.

Deviations of S-T Segment

Depression of the S-T segment has long been associated with hypokalemia.[26, 27, 29–31, 33–36, 64] Depression of S-T segment is of particular value when it is present in leads V_1 to V_3 in a patient who shows evidence of left ventricular hypertrophy or strain. One would normally expect some elevation of S-T segment in these leads and the presence of an isoelectric or depressed S-T segment in leads V_1 to V_3 should cause one to suspect the presence of hypokalemia.

Ratio of Serum Sodium to Potassium

There has not been good agreement concerning the relationship of the electrocardiogram to the ratio of serum sodium to potassium. Rosen[65] has suggested that the relationship of serum sodium to potassium is more important than the actual absolute concentration of potassium in the serum. Others,[24] however, have found little or no correlation between the sodium-potassium ratio and electrocardiographic changes. Still others[27, 40, 61] have suggested an indirect relationship between sodium, potassium, and electrocardiographic changes; for example, in those clinical states in which the serum pH is abnormal

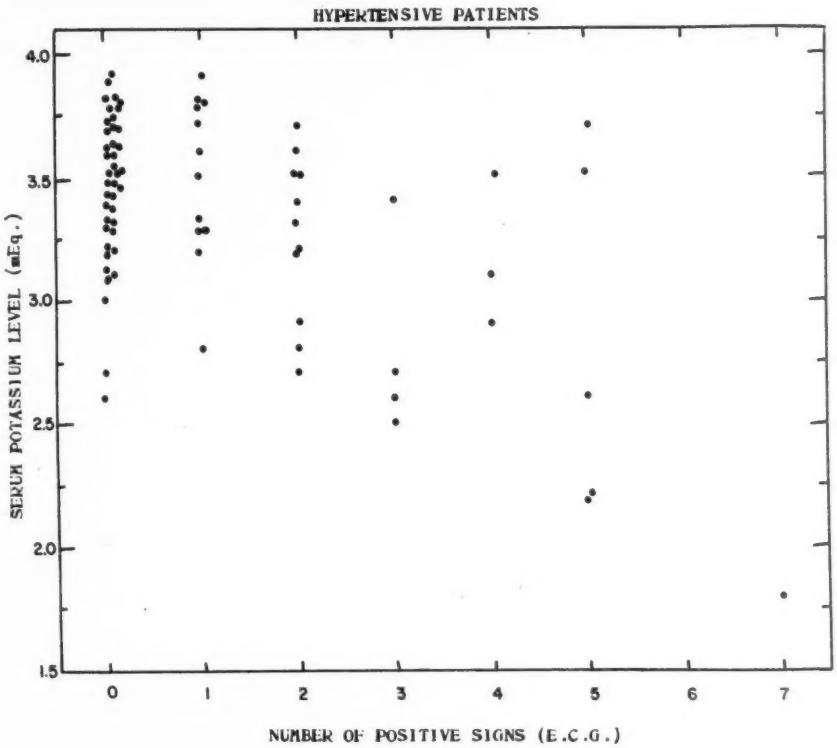

Figure 10

Correlation between electrocardiographic criteria (table 5) and serum potassium concentration in hypertensive patients.

there is often associated abnormality of either one or both of these ions.

If one uses the normal range of 25 to 40 for the sodium-potassium ratio, electrocardiographic changes would be expected if the ratio were greater than 40 (relative hypokalemia). As shown in figure 8 this would mean that the electrocardiographic changes of hypokalemia should be noted at values less than approximately 3.3 mEq. Certainly changes may be seen at this level and even above it but by no means with any degree of regularity. Thus, we feel that the sodium-potassium ratio is simply another factor in the production of electrocardiographic changes but certainly not the main one.

Acid-Base Balance

The discussion of this paper would not be complete without a consideration of the metabolic states of alkalosis and acidosis. It may be that the serum pH, with or without coexisting alterations of serum cations and anions, may be the main factor in the production of the electrocardiographic changes currently attributed to hypokalemia and hyperkalemia. As early as 1932 it was shown that an "excess of CO_2 increases the size of the T wave in all leads. . . ."[66]

In 1939 Barker and associates[67] reported that alkalosis (by hyperventilation or ingestion of sodium bicarbonate) is accompanied by a decreased amplitude of the T wave. Similarly acidosis was found to increase the T-wave amplitude. In a study of patients with diabetic acidosis, Nadler and associates[53] noted that T-wave amplitudes decreased as the serum pH increased and similarly as the carbon dioxide pressure (pCO_2) increased. In 1953 Magida and Roberts found that they could produce hypokalemic electrocardiographic

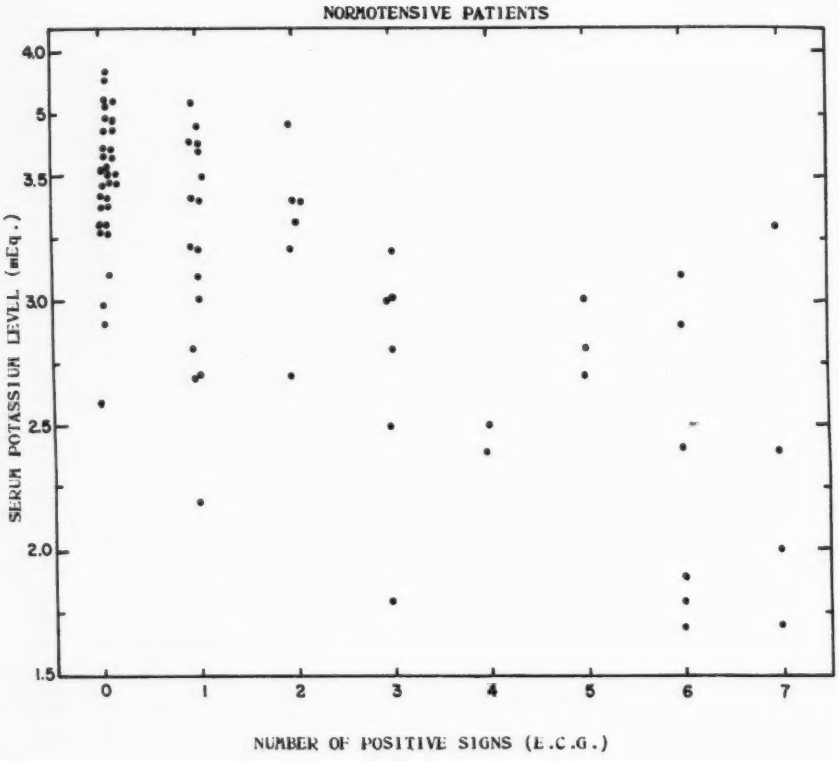

Figure 11

Correlation between electrocardiographic criteria (table 5) and serum potassium concentration in normotensive patients.

changes in dogs by increasing the serum pH, bicarbonate, and sodium even though the serum potassium remained normal.[40, 41] No electrocardiograms of hypokalemia were shown and their only comment on the pattern was "sequential lowering and inversion of the T wave. . . ." They expressed the opinion that the transmembranous gradient of hydrogen ion is the important factor in the bioelectric phenomena of the heart. Bellet in 1955[27] pointed out that hypopotassemia is often associated with alkalosis. Alkalosis is associated with increased serum pH, increased serum sodium, decreased phosphate and increased carbon dioxide combining power; it also tends to affect the serum calcium by means of alteration of the solubility product, so that the result is a normal or low concentration of serum calcium which could also affect the electrocardiogram.

Scribner and associates[68] have emphasized the importance of the ratio of extracellular potassium to intracellular potassium. They suggest that alkalosis causes a shift of potassium into the cell and consequently a decrease in the ratio of extracellular to intracellular potassium. Acidosis causes an opposite effect. It is in this way then, that acid-base imbalance profoundly affects the concentration of serum potassium. This may be one factor involved in the poor correlation between total body potassium and serum potassium. Thus hypokalemia in a patient with acidosis might indicate severer depletion of potassium than a similar degree of hypokalemia in a patient with alkalosis.

In 1953 it was pointed out[69] that often in severe and chronic hypokalemic states, the

electrocardiogram may not return to normal for more than a week, even though the repletion of potassium seems to have been well managed. At that time it was suggested that perhaps this was due to some organic change in the myocardial cells — perhaps similar to organic changes produced by experimental potassium deficiency.

In a report of a case of primary aldosteronism van Buchem[70] noted that after removal of hyperplastic adrenal glands the serum potassium returned to normal in several days. However, the electrocardiogram showed typical hypokalemic changes for 5 weeks. It was then mentioned (without implying a relationship to the electrocardiogram) that acid-base balance and carbohydrate metabolism did not return to normal for "several weeks." In our own series the marked electrocardiographic effects of acid-base equilibrium are clearly shown in a few cases in which carbon dioxide determinations were available (figs. 5 and 9).

In the past it has not been clear why different patients with the same concentration level of serum potassium show different electrocardiographic changes. Bellet[27] has suggested that because the normal concentration of serum potassium[71] of patients varies from 3.6 to 5.6 mEq., a patient with a normal value for potassium of 5.5 mEq. would, in a relative sense, be more deficient at a level of 3.4 mEq. than would a patient with a normal value for serum potassium of 3.7 mEq. Such an explanation does not obtain, however, when one considers electrocardiograms and serial serum potassium changes solely in the hypokalemic ranges.

It has also been suggested that the rate of change of serum potassium is important, but, as was indicated in our method of procedure, this factor was minimized in our study. Ringer[12] in 1883 showed similar effects of rubidium and potassium on the heart. Tarail[72] recently suggested the importance of this and other trace elements as possible additional factors in electrocardiographic changes seen with hypokalemia. Young and Daugherty,[73] using hemodialysis to accomplish acute potassium depletion, showed that S-T depression

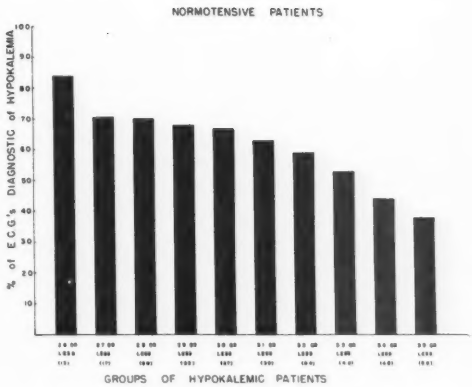

Figure 12

Cumulative grouping of normotensive patients in relation to serum potassium concentration in milliequivalents. The electrocardiograms of the various groups were then evaluated with the criteria in table 5.

seemed more closely related to the quantity of potassium removed rather than to the concentration of potassium in the plasma. Exactly what the electrocardiogram reflects then is unclear. Certainly, the potassium metabolism and acid-base balance play major roles.

Electrocardiographic Criteria for Hypokalemia

With the understanding that the relationship between the electrocardiogram and the afore-mentioned factors is not clearly defined, the electrocardiographic criteria of hypokalemia shown in table 5 are proposed.

These criteria were obtained from data in this study. They pertain only to normotensive patients, since the presence of hypertension has been shown to obscure many of the electrocardiographic signs (fig. 10). It is to be emphasized that these criteria are to be used in a positive sense; that is, when the electrocardiogram scores 3 or more points the diagnosis of hypokalemia is almost certain. However, if the electrocardiogram scores less than 3 points, or even no points, this does not rule out the possibility of hypokalemia (figs. 10 and 11).

As shown in figure 12, the electrocardiographic diagnosis of hypokalemia in normotensive patients is fairly secure at the lower concentrations of serum potassium. In the literature much emphasis has been placed on

certain levels below which the electrocardiogram will be diagnostic of hypokalemia. It has been one of the purposes of this paper to show the multiple factors that affect the electrocardiogram in hypokalemic and normokalemic states.

Summary

A definite correlation can be established between the electrocardiogram and the serum potassium level at hypokalemic levels. A study was made at the Mayo Clinic of 130 hypokalemic patients with relatively stable clinical states. Variations in Q-T intervals, P-R intervals, atrial rhythm, P waves, T/R values, and T-wave and U-wave contour in hypokalemia were noted as were the relationships between the T-U complex, electrical repolarization phenomena and potassium metabolism. Since modifying factors such as drugs, certain electrolyte disturbances, variations in cardiac rate, conduction defects, and myocardial ischemia were eliminated by careful selection of patients, only the influence of acid-base imbalance, sodium-potassium ratio, and hypertension on the electrocardiogram was studied. Acid-base imbalance and hypertension often simulated or obscured electrocardiographic evidence of hypokalemia.

Electrocardiographic criteria of hypokalemia include various combinations of the following signs: (1) T/U value of 1 or less in lead II or V_3, (2) U-wave amplitudes of greater than 0.5 mm. in lead II or greater than 1 mm. in V_3, and (3) S-T depression of 0.5 mm. or more in lead II or leads V_1, V_2, and V_3. It must be remembered that a normal electrocardiogram does not exclude hypokalemia and that an electrocardiogram which fulfills the established criteria does not necessarily indicate hypokalemia unless the factors discussed have been eliminated or minimized.

Summario in Interlingua

Un definite correlation pote esser establite inter le electrocardiogramma e le nivello seral de kalium quando le cifras pro isto representa valores hypokaliemic. Esseva effectuate al Clinica Mayo un studio de 130 patientes hypokaliemic in relativemente stabile statos clinic. Variationes in le intervallos Q-T, in le intervallos P-R, in le rhythmo atrial, in le undas P, in le valores T/R, e in le contornos del undas T e U esseva notate, si ben como etiam le relationes inter le complexo T-U, le phenomenos de repolarisation electric, e le metabolismo de kalium. Le meticulose selection del patientes garantiva le exclusion de factores modificatori como drogas, certe disturbationes electrolytic, variationes del frequentia cardiac, defectos de conduction, e ischemia myocardial, de maniera que solmente le influentia del imbalancia de acido e base, del proportion de natrium a kalium, e de hypertension esseva includite in le studio del electrocardiogramma. Imbalancia de acido a base e hypertension frequentemente simulava o obscurava le evidentia electrocardiographic de hypokaliemia.

Le criterios electrocardiographic de hypokaliemia include varie combinationes del sequente signos: (1) Valores pro T/U de 1 o minus in derivation II o derivation V_3, (2) amplitudes del unda U de plus que 0,5 mm in derivation II o de plus que 1 mm in derivation V_3 e (3) depression de S-T de 0,5 mm o plus in derivation II o in le derivationes V_1, V_2, e V_3. On debe rememorar se que un electrocardiogramma normal non exclude hypokaliemia e que un electrocardiogramma que satisface le establite criterios non indica necessarimente le presentia de hypokaliemia, excepte si le supra-discutite factores ha essite eliminate, o si lor signification ha essite reducite a un minimo.

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On Cardiac Murmurs

By AUSTIN FLINT, M.D.

The significance of organic murmurs is limited to the points of information already stated in the introductory remarks, viz., the existence of lesions, their localization, and the fact of valvular insufficiency or regurgitation. Whether the lesions involve immediate danger to life, or, on the contrary, are compatible with many years of comfortable health, the murmurs do not inform us, nor do they teach us how far existing symptoms are referable to the lesions, and how far to functional disorder induced by other morbid conditions. Neither the intensity nor the quality of sound in the murmurs furnish any criteria by which the gravity of the lesions or their innocuousness can be determined. A loud murmur is even more likely to be produced in connection with comparatively unimportant lesions than with those of a grave character, because in the former, rather than in the latter case, is the action of the heart likely to be strong, and the intensity of the murmur, other things being equal, will depend on the force with which the currents of blood are moved. Whether the murmur be soft, or rough, or musical, depends not on the amount of damage which the lesions have occasioned, but on physical circumstances alike consistent with trivial and grave affections.—*Am. J. M. Sc.* n.s. **44**: 29, 1862.

Serum Lipoproteins in Patients with Intermittent Claudication and Myocardial Infarction

By P. J. NESTEL, M.B., B.S. (Sydney), MRACP

IN THE investigation of atherosclerosis it is frequently implied that clinical evidence of involvement of one part of the arterial tree, such as the coronary arteries, indicates a general state of atherosclerosis. Since this view is not necessarily correct, it seemed important to study some features of lipid metabolism in patients whose clinical indication of atherosclerosis was occlusion of an arterial territory other than the coronary, and to compare them with findings in patients with symptoms of coronary artery disease and in subjects with no clinical evidence of arterial disease. Patients with intermittent claudication were chosen. In such patients Barker[1] found a higher serum cholesterol and total lipids than in controls of similar age. However Azen et al.[2] measured low-density lipoproteins in 84 patients with intermittent claudication and found that 57 per cent had normal values and only 25 per cent were definitely outside their normal range.

Material and Methods

Four groups of patients were studied. Group 1 comprised 44 male patients with occlusive arterial disease of the legs. They had clinical evidence of severe involvement of the arteries of both legs, which was confirmed by femoral arteriography. Patients with diabetes mellitus, essential hypercholesterolemia, and those with clinical evidence of a major arterial occlusion within the past 6 months were excluded. Their average age was 61, with a standard deviation of 7.4 years.

Group 2 comprised 61 men who were matched with group 1 for age and who had no symptoms or signs of coronary or peripheral arterial disease. Their average age was 63, with a standard deviation of 8.1 years.

Group 3 comprised 30 male patients who had had a myocardial infarction 3 to 4 weeks previously and who had no evidence of arterial disease elsewhere. Their average age was 49, with a standard deviation of 7.2 years. They were all on a normal diet, and after an initial 2 days on heparin were receiving phenindione.

Group 4 comprised 30 inmates of a home for elderly men who were studied because of the possible relevance of lack of exercise. They all led a sedentary life and had no symptoms or signs referable to their cardiovascular system. Their average age was 65, with a standard deviation of 8.1 years.

Serum lipoproteins were separated by electrophoresis, stained with Sudan black B, and scanned.[3] Since other workers[4] have found that in coronary artery disease beta lipoproteins are raised and alpha lipoproteins lowered, the beta/alpha ratio was the index measured.

Results

Figure 1 shows the frequencies of distribution of the different beta/alpha lipid ratios in the 4 groups. The mean ratio for each group is shown in table 1 and the ratios are compared in table 2. The mean ratio for patients in group 1 is significantly higher than for the other groups, which do not differ significantly from each other.

The comparison of mean ratios does not fully describe the differences between the groups because the frequency distributions depart somewhat from the normal Gaussian form. Differences between group 1 and the other groups are further shown by differences in modal values and in the relative numbers of rather high ratios in group 1. Nevertheless there is considerable overlap between ratios in the 4 groups.

Since the mean age for group 3 was lower than for group 1, the possibility was consid-

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Supported in part by a grant from the National Health and Medical Research Council of Australia.

ered that this difference in age might account for the lower lipid ratios in group 3. Calculation showed, however, that there was a significant negative regression between lipid ratios and age in group 3, the ratios decreasing by 0.02 per year from ages 32 to 73. A similar calculation for the patients in the other 3 groups showed no significant regression.

Discussion

These results show that as a group, patients with symptoms of arterial occlusion of the main arteries of the legs differ from patients with symptoms due to occlusion of the coronary arteries and from people of similar age with no symptoms of arterial occlusion, in having relatively high beta/alpha lipid ratios in their blood. Since they differ in the same way from men of similar age whose exercise is restricted for other reasons, this is not simply the consequence of lack of exercise.

The difference between the normal controls and the patients with coronary occlusion is almost significant but 2 points merit consideration. Firstly, Dodds and Mills[5] showed that myocardial infarction is itself associated with significant lipoprotein abnormalities that persist for at least 8 weeks, and since the patients in the present study were investigated 3 to 4 weeks after their myocardial infarction, their lipid ratios may have later returned to lower levels. Secondly, the group of patients with myocardial infarction included many elderly subjects and this would tend to lower the lipid ratio for the group. The significant negative regression between lipid ratios and age in this group is in agreement with the findings of Oliver and Boyd[6] that in coronary artery disease the greatest increase in plasma lipids occurred in the younger age groups. This does not appear to be a feature of patients with intermittent claudication or subjects without symptoms of vascular occlusion.

There are several possible interpretations of these findings. The high beta/alpha lipid ratios in patients with intermittent claudication might reflect more extensive and severe atherosclerosis than exists in patients with myocardial infarction and in those with no

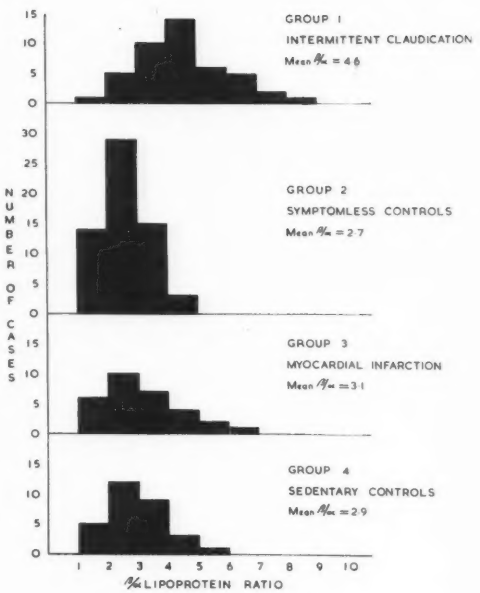

Figure 1

Beta/alpha lipid ratios in patients with myocardial infarction, intermittent claudication, and controls.

clinically evident arterial occlusions. This seems unlikely, since evidence from necropsy and radiologic studies suggests that the populations from which these groups were selected may not differ strikingly in the extent of atherosclerosis in the arteries of the legs.[7, 8] Since the patients with intermittent claudication do, however, differ from comparable people without symptoms in the extent and severity of thrombotic arterial occlusions in their legs,[9] it is possible that their beta/alpha lipid ratios are more directly related to intra-arterial thrombosis. It is interesting that fibrinolytic activity in these patients is also markedly depressed compared with patients of the same age without clinical evidence of occlusions,[10] but is normal in patients who had recovered after a myocardial infarction.[11] The groups of patients studied may vary therefore in their liability to intravascular thrombosis.

Conclusive evidence of this would have to come from the study of the natural histories of the 2 diseases. Such studies as are available

Table 1

Mean Beta/Alpha Lipid Ratios and Their Standard Deviation

Group	Number	Mean ratio ± standard deviation
1. Intermittent claudication	44	4.6±0.22
2. Symptomless controls	61	2.7±0.11
3. Myocardial infarction	30	3.1±0.24
4. Sedentary controls	30	2.9±0.17

Table 2

Comparisons of Differences between Mean Beta/Alpha Lipid Ratios

Groups compared	Difference between means	Standard error of difference	Significance
1 and 2	1.89	0.2455	$p<0.001$
1 and 3	1.46	0.3243	$p<0.001$
1 and 4	1.69	0.2764	$p<0.001$
2 and 3	0.43	0.2619	$0.05<p<0.1$
2 and 4	0.20	0.1982	$0.2<p<0.3$
3 and 4	0.23	0.2910	$0.3<p<0.4$

are difficult to interpret. Patients with intermittent claudication frequently suffer thrombosis of cerebral or coronary arteries. Hines and Barker[12] reported that half of their patients died within 3 years, the majority from coronary occlusion, and Francis and Barnett's[13] experience in Australia was similar. McDonald[14] also found in a 2-year follow-up period that 31 of 79 patients with intermittent claudication complained of angina pectoris or had abnormal electrocardiographs. On the other hand, only 4 of 50 patients with angina pectoris also complained of intermittent claudication, and a further 8 had tonoscillographic evidence but no symptoms of arterial occlusion of the legs. Although it may appear from the above studies that patients with intermittent claudication are more liable to occlusion in another arterial territory than are patients with angina pectoris, the follow-up period was insufficient to determine whether the 2 conditions differed. It would be interesting to follow some of the biochemical abnormalities in individuals in each group in relation to the development of the alternative condition in them.

A third possibility is whether atherosclerosis in different arterial territories is governed by different factors. It has been shown that the administration of estrogens will reduce the severity of atherosclerosis in the coronary artery and not in the aorta.[15] The serum cholesterol level was shown to be related to the degree of coronary thrombosis and to the cholesterol content of the coronary artery,[16] but not to the cholesterol content of the aorta.[17] A good correlation was found between age and the severity of atherosclerosis in the femoral artery, but not in the coronary artery.[18] The finding of a high beta/alpha lipid ratio in patients with intermittent claudication may further reflect the fact that the same factors do not necessarily govern the occurrence of occlusive arterial disease in different territories.

Summary

The serum beta/alpha lipid ratios were estimated by electrophoresis in 4 groups of people. These comprised 44 male patients with intermittent claudication; 61 men who were matched for age with the previous group and who were clinically free of cardiovascular disease; 30 male patients who had recently had a myocardial infarction; and a further group of 30 male controls whose physical activity was limited by factors other than disease.

The highest mean serum beta/alpha lipid ratio was found among the patients with intermittent claudication and was very significantly higher than the ratios found among the other 3 groups. The difference in the ratios between the patients with myocardial infarction and the 2 control groups was not significant.

These differences and in particular the difference in the ratios between the patients with myocardial infarction and intermittent claudication are discussed.

Acknowledgment

I wish to thank Professor R. R. H. Lovell for advice and encouragement, and Dr. T. E. Lowe, Director, and Dr. A. J. Barnett, Associate Director, of the Baker Medical Research Institute, Melbourne, where part of this work was commenced.

Summario in Interlingua

Le proportion de lipido beta a alpha in le sero esseva estimate electrophoreticamente in 4 gruppos de subjectos. Istos esseva (1) 44 patientes mascule con claudication intermittente, (2) 61 subjectos mascule appareate in etate con le previe gruppo e clinicamente libere de morbo cardiovascular, (3) 30 patientes mascule que habeva recentemente habite un infarcimento myocardial, e (4) 30 subjectos mascule, serviente como gruppo de controlo, con restriction de activitate physic in consequentia de factores altere que morbos clinic.

Le plus alte valor medie pro le proportion de lipido beta a alpha in le sero esseva incontrate in le patientes con claudication intermittente; isto esseva significativissimemente plus alte que le proportiones trovate in le altere 3 gruppos. Le differentia inter le proportiones in patientes con infarcimento myocardial e in le 2 gruppos de controlo non esseva significative.

Le differentias observate es discutite, specialmente le differentia inter le proportion in patientes con infarcimento myocardial e illo in patientes con claudication intermittente.

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Lipoproteins Quantitated by Paper Electrophoresis as an Index of Atherosclerosis

By Moses Wurm, M.S., Robert Kositchek, M.D., and Reuben Straus, M.D.

NUMEROUS studies have been devoted to the diagnosis of coronary atherosclerosis in the absence of classical clinical signs and symptoms. These studies have emphasized the relationship of blood lipids to atherogenesis.[1] Serum cholesterol, phospholipids, and cholesterol/phospholipid ratios have been employed for diagnostic purposes with questionable success. A more reliable index for distinguishing atherosclerotic patients from normal individuals has been claimed for the lipoproteins per se, or their cholesterol content, separated by chemical fractionation,[2] ultracentrifugal flotation,[3, 4] and starch and moving boundary electrophoresis.[5, 6]

For routine clinical use the lipoprotein procedures are almost, if not entirely, unavailable. A practical solution for this problem has been the development of the paper electrophoretic procedure for such separation of serum lipoproteins by Swahn[7] and Jencks et al.[8] Heretofore, these methods have not been found to be sufficiently reliable.[9,10]

A new procedure for separating 5 lipid-containing fractions of serum by paper electrophoresis and a method of quantitation have been reported from our laboratory.[11] It is the purpose of this report to present the results of an initial study correlating lipoprotein distributions in "normal" individuals and in atherosclerotic patients.

Material and Method

The present series consists of 40 consecutive, unselected patients classified as abnormal on the basis of unequivocal evidence of one or more myocardial infarctions or arteriosclerotic cerebrovascular accidents. In addition, many of these patients presented ancillary clinical symptoms of cardiovascular disease such as angina, hypertension, nephrosclerosis, retinopathy, arteriosclerotic gangrene, and positive familial histories of coronary disease. Three patients in this group also exhibited xanthomata with familial and refractory hypercholesteremia. In this group there were 32 males, ranging in age from 38 to 74 years, with a mean age of 55 years, and 8 females, ranging in age from 31 to 70 years, with a mean age of 54 years.

Another group of 40 individuals selected in the same manner, represent the controls (normal). These were so classified by the exclusion of atherosclerotic cardiovascular disease on the basis of negative findings on routine history and physical examination and by electrocardiography. While this group of "normals" consisted chiefly of healthy individuals, some patients with nonrelated disease were included and admittedly some degree of asymptomatic atherosclerosis may be presumed to be present. This group is represented by 25 males ranging in age from 10 to 80 years, with a mean age of 48 years, and 15 females ranging from 11 to 70 years, with a mean age of 34 years. Since this experiment was set up on a blind basis, initially 2 children, one of each sex, were included. If these are omitted, the age distribution for males is 33 to 80, with a mean age of 49 years, and for females 23 to 70, with a mean age of 47 years.

The usual clinical evaluation also included laboratory examinations such as complete blood counts, urinalysis, serum protein-bound iodine, liver-function tests, blood glucose, serum urea nitrogen and uric acid, blood serologic tests, and Papanicolaou tests of vaginal exfoliated cells. The results of these tests were found to be noncontributory and are not further considered.

Fasting blood specimens were drawn in the early morning and all analytical procedures were started within 24 hours. The lipid spectrum for each individual was determined as follows: the concentration of cholesterol in the serum was measured by the method of Abell et al;[12] lipid phosphorus was assayed on Bloor extract of serum by a modification of the method of Fiske and Subbarow[13] and

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Supported in part by a grant from Searle and Company.

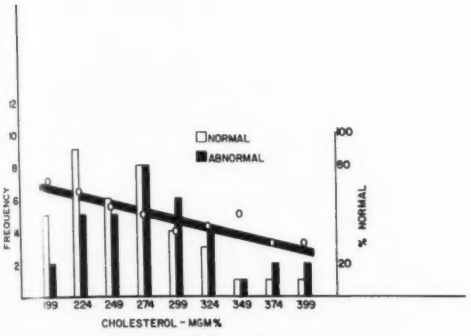

Figure 1

Frequency distribution of cholesterol values in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

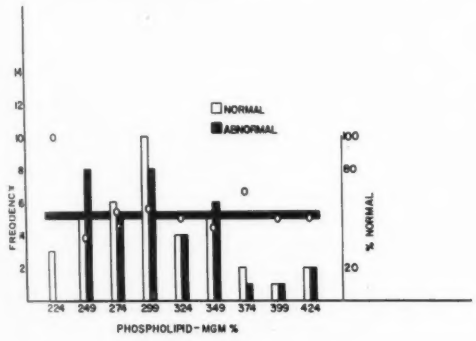

Figure 2

Frequency distribution of phospholipid values in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

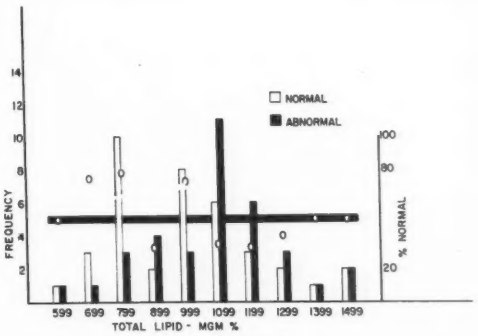

Figure 3

Frequency distribution of total lipid values in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

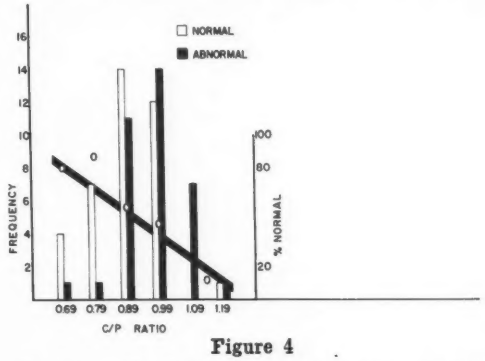

Figure 4

Frequency distribution of cholesterol/phospholipid ratio in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

converted to phospholipids by a factor of 25; and total lipids were estimated gravimetrically by a modification of the method of Sperry.[14] The apparatus and technic of paper electrophoresis routinely employed in this laboratory during the last 4 years, together with our method for visualizing lipoproteins with Fat Red 7 B and direct scanning of the electrophoretic pattern for purposes of quantitation, have been previously reported.[11, 15] With this technic 5 lipoprotein fractions can be demonstrated, namely; lipalbumin, alpha-1 lipoprotein, alpha-2 lipoprotein, beta lipoprotein, and gamma lipoprotein plus neutral fat fractions, which are evaluated in terms of relative concentration. Beta/alpha ratios were calculated by dividing the beta lipoprotein value, exclusive of the gamma plus neutral fat fraction, by the combined values of alpha-2, alpha-1, and lipalbumin fractions. Beta/lipalbumin ratios were derived similarly from the values of these individual fractions.

Statistical constants were calculated according to standard methods.[16] Significance of differences between groups was determined by the Fisher *t* test, for which a value of 3.0 or more was considered by us to be acceptable.

Each type of datum also was examined for its significance in predicting the atherosclerotic status of the individual. For this purpose, the percentage of normal individuals was determined at each level of the variable being examined. Two levels of confidence are considered, namely, the 100 per cent level, at which all individuals without exception can be classified as either "normal" or abnormal, and the 80 per cent level for such individual

Table 1

Lipid and Lipoprotein Values in Coronary Atherosclerotic Patients and Symptomless Controls

	Group				Group differentiation		Individual differentiation					
	Control		Abnormal				100 per cent confidence Limiting values			80 per cent confidence Limiting values		
Blood fraction	No. of subjects	Mean and standard deviation	No. of subjects	Mean and standard deviation	Fisher t test	Significant	Per cent of population	Less than	More than	Per cent of population	Less than	More than
Cholesterol*	38	248±53.6	35	273±60.4	1.85	no	7	159	432	14	178	354
Phospholipid*	38	292±49.7	35	296±50.7	0.337	no	10	225	420	0	—	—
Total lipid*	38	946±255	35	1066±384	1.54	no	0	—	—	0	—	—
Cholesterol/ phospholipid	38	.85± 0.12	35	0.92± 0.09	2.32	no	8	65	—	33	0.80	1.00
Lipalbumin†	40	19.8 ± 5.86	40	13.2 ± 3.96	5.78	very, .001	32	10.4	21.5	56	12.7	17.7
Alpha-1 lipoprotein†	40	4.67± 2.07	40	3.80± 1.43	2.17	no	12	2.2	7.0	22	2.3	6.5
Alpha-2 lipoprotein†	40	7.06± 2.35	40	5.07± 1.86	4.14	very, .001	11	2.7	9.6	55	4.8	7.4
Beta/lipoprotein†	40	52.5 ± 9.20	40	62.5 ± 8.84	4.88	very, .001	15	46.8	76.5	40	51.1	70.7
Gamma plus neutral fat†	40	15.5 ± 4.56	40	15.4 ± 6.78	0.023	no	3	7.2	—	14	9.5	—
Beta/alpha	40	1.81± 0.68	40	3.22± 1.48	5.41	very, .001	22	1.54	4.72	65	2.00	2.62
Beta/lipalbumin	40	3.02± 1.36	40	5.55± 3.11	4.65	very, .001	32	2.56	6.82	51	2.97	5.12

*Mg. per cent concentration.
†Relative per cent concentration.

classification, which allows for a possible error of 1 in 5.

Results

Cholesterol

The data for serum cholesterol values in 73 individuals of the combined sample population are compiled in the histogram (fig. 1). It will be noted that the frequency distribution of this serum component shows a relatively poor normal distribution for either the group of controls or the abnormal individuals, and is also true for the combined population. The reason for this deviation is not apparent because there are many factors, not considered in the present study, that may contribute to the concentration of blood cholesterol. When the 2 groups, "normal" and atherosclerotic, are compared statistically it is found that they are different only on a 5 per cent confidence level ($t = 1.85$) (table 1). This is not considered sufficiently significant by our criteria.

The continuous graph also shown in figure 1 depicts the per cent of "normal" individuals found at each level of serum cholesterol. It will be noted that at the extreme low value of 199 mg. per cent, the chances are 3 to 1 that the subject is normal. With increasing concentration of serum cholesterol, the chance of finding a normal individual progressively decreases, so that one who displays a serum cholesterol level in the vicinity of 399 mg. per cent is favored to be an atherosclerotic by a 2 to 1 ratio. By extrapolation, it becomes apparent also that the confidence with which normal and atherosclerotic subjects can be identified increases rapidly as serum cholesterol levels continue to decrease or increase. At approximately 135 and 475 mg. per cent only "normal" and abnormal, individuals respectively, may be encountered. Actually our data show that an absolute determination of "normal" can be made at cholesterol values below 159 mg. per cent and a diagnosis of atherosclerosis at values above 432 mg. per cent. These limits however apply

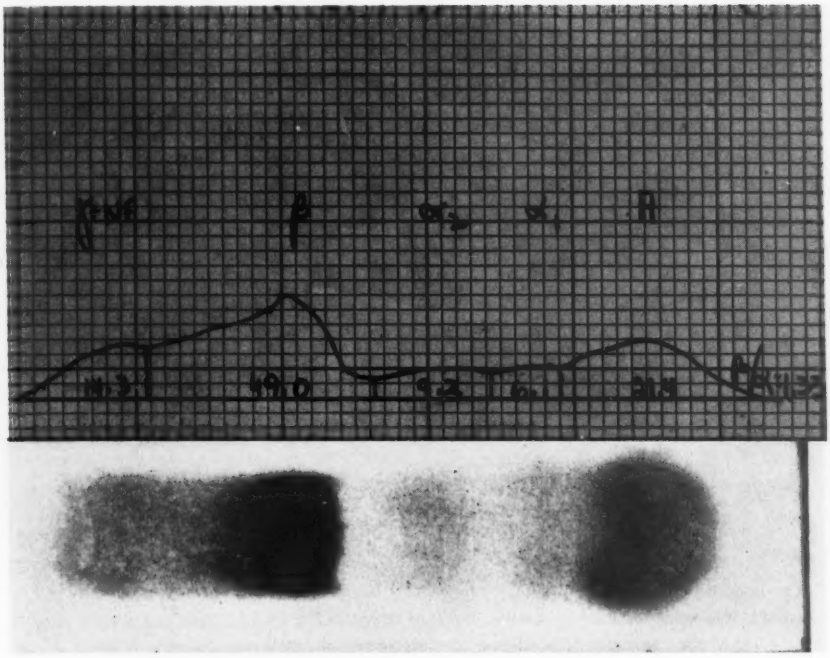

Figure 5

Representative electrophoretic pattern of serum lipoproteins with density distribution curve.

to only 5 individuals, or 7 per cent of the sample tested. Below a cholesterol level of 178 mg. per cent and above 354 mg. per cent an individual can be correctly classified 80 per cent of the time. This level of confidence applies to 10 individuals only, or 13 per cent of the population tested.

Phospholipids

Figure 2 illustrates the frequency distribution of phospholipid values. It will be noted that both "normal" and abnormal patients are almost equally distributed at every level of phospholipid concentration. The high degree of overlapping values for both groups is reflected also by the low t value of 0.34, (table 1), indicating no significant difference. It is apparent that the predictive value of serum phospholipid concentration for the individual is extremely low, since only 7 patients, or 10 per cent of the sample population can be distinguished absolutely as normal or atherosclerotic. This occurrence, furthermore, is considered to be purely fortuitous, since no concentration ranges can be found in which a portion of the population can be classified on an 80 per cent confidence level, and no significant trend in the distribution of values can be identified.

Total Lipids

Serum total lipid concentrations appear to be the least meaningful of all determinations. From figure 3 and its statistical data (table 1) it is evident that these values for the 2 groups of patients are not significantly different and that no diagnostic inference for the individual can be found. This is emphasized particularly by the observation that both the highest and the lowest values of serum lipids were found in abnormal patients.

Cholesterol/Phospholipid Ratio

Comparison of figures 1 and 4 reveals a striking similarity in the frequency distribu-

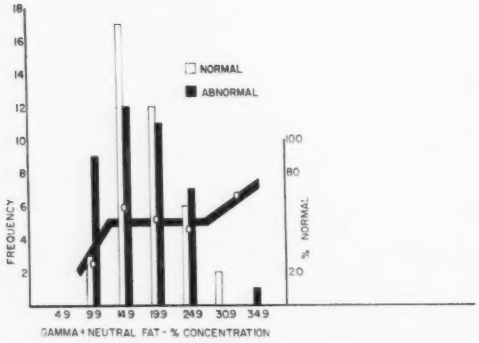

Figure 6

Frequency distribution of gamma plus neutral fat values in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

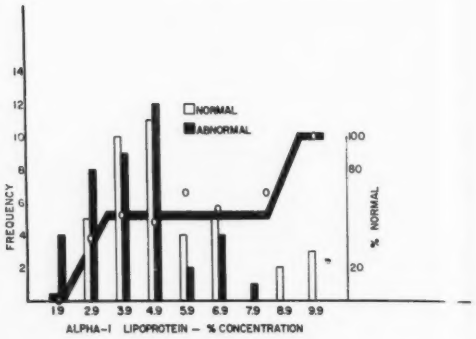

Figure 7

Frequency distribution of alpha-1 lipoprotein values in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

tion of cholesterol values and cholesterol/phospholipid ratios. From the calculated Fisher t value it will be noted that the difference in this variable between normal and abnormal groups (table 1) is of a low order of significance. Only 2 individuals, or 3 per cent of the entire sample, with cholesterol/phospholipid ratios below 0.65 can be differentiated with absolute confidence. If one accepts an 80 per cent chance of classifying an individual, then 24 persons, or 33 per cent of the population with cholesterol/phospholipid values less than 0.80 and greater than 1.00 can be differentiated correctly.

Lipoproteins

Electrophoretic strips stained with Fat Red 7B reveal the presence of 5 lipid fractions,[7] which are illustrated in figure 5. It is of interest to examine these fractions individually and in combination for the degree to which they correlate with manifest coronary artery disease and, conversely, the extent to which they can be used as a diagnostic index.

Gamma Lipoprotein Plus Neutral Fat Fraction

The least significant of all the variables measured in this portion of the study appears to be the gamma lipoprotein and neutral fat fraction. Figure 6 and the related statistical data (table 1) reveal a marked overlapping in the frequency distribution of the "normal" and atherosclerotic groups. The skewness of the distribution observed in the entire sample population probably is associated with the age and diet of these patients. Since the percentage of "normals" at each concentration level of this fraction approximates 50 per cent as shown by the line graph, it is concluded that this has a low predictive value for classifying the individual. Actually, only 2 (3 per cent) and 11 (14 per cent) persons in our sample population can be classified on an absolute and on an 80 per cent confidence level, respectively. This result is not unexpected, since it probably reflects the low order of diagnostic significance found for the serum total lipids described above.

Alpha-1 Lipoprotein

The analysis of our data dealing with alpha-1 lipoprotein concentration is summarized in figure 7. Although the difference in mean concentration between the "normal" and abnormal groups is more significant ($t = 2.17$) than that found for any of the chemically determined variables, the data still do not satisfy our criteria for acceptance. Twelve per cent of the population can be identified with absolute certainty as "normal" or atherosclerotic when alpha-1 lipoprotein values are below 2.2 and above 7.0 per cent. If confidence limits of 4 to 1 are acceptable, then relative con-

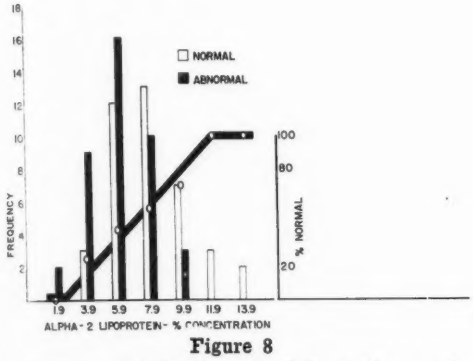

Figure 8

Frequency distribution of alpha-2 lipoprotein values in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

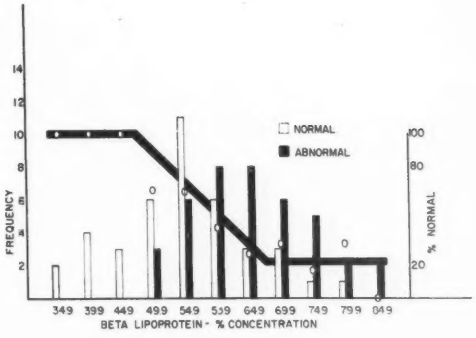

Figure 9

Frequency distribution of beta lipoprotein values in patients with manifest coronary disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

centration of this lipoprotein fraction below 2.3 and above 6.5 per cent will include 18 individuals or 22 per cent of the population.

Alpha-2 Lipoprotein

The distribution of the relative concentrations of alpha-2 lipoproteins is shown in figure 8. It will be noted that each group, as well as the total population, displays a well-normalized frequency distribution. Although a considerable degree of overlapping is noted, comparison of the mean values for the 2 groups is found to be significantly different (t = 4.14). In addition, the possibility of differentiating "normal" from abnormal on an individual basis is considerably increased since 55 per cent of the total population can be classified with 80 per cent reliability, whereas only 11 per cent of the sample can be classified with absolute assurance.

Beta Lipoproteins

Our findings with respect to the relative concentrations of beta lipoproteins are shown in figure 9. The range of values for the entire population as well as for each group of patients closely assumes a normal distribution curve. On a group basis, normal individuals can be satisfactorily differentiated from atherosclerotic patients, since the difference in the mean values for each is highly significant (t = 4.88). For the purpose of classifying individuals, beta lipoprotein values are approximately as satisfactory as alpha-2 lipoproteins.

Lipalbumin

The relative concentrations of lipalbumin are graphically presented in figure 10, from which it can be seen that overlapping values for the "normal" and abnormal subjects occur in a narrow portion of the entire range and include a relatively small fraction of the entire population. It appears possible to identify the atherosclerotic status of an individual with absolute certainty if the lipalbumin concentration is below 10.4 or above 21.5 per cent. The tail-ends of the distribution beginning with these values include 26 individuals, or 32 per cent of the sample. If one accepts a 4 to 1 probability for correct diagnosis, then 56 per cent of the population can be satisfactorily classified when the concentration is below 12.7 and above 17.7 per cent. The calculated Fisher's t of 5.78 also indicates that the difference in the means for the 2 groups is highly significant.

Beta/Alpha Ratio

The distribution of the beta/alpha ratios for "normal" and patients with manifest coronary artery disease is shown in figure 11. To conform with the beta/alpha ratios published by others[17, 18] the lipalbumin, alpha-1,

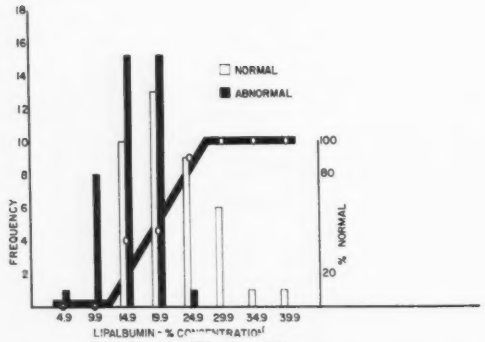

Figure 10

Frequency distribution of lipalbumin values in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each concentration level.

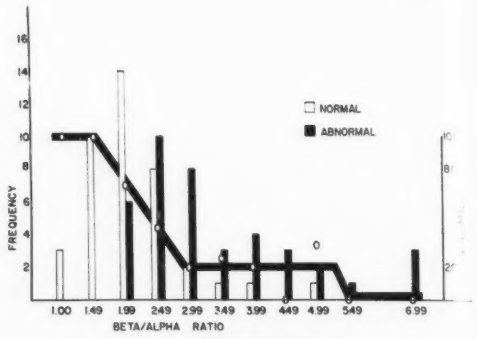

Figure 11

Frequency distribution of beta/alpha ratios in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each level of values.

and alpha-2 lipoprotein fractions are included in the "alpha" portion of this ratio. It will be noted that this value in our group of normal subjects shows a typical Gaussian distribution, except for a marked tailing toward the higher values. This undoubtedly reflects the uncertainty in the classification of "normal" individuals on clinical evidence alone. The group of abnormal individuals shows a similar tailing toward higher values. Nevertheless, these 2 groups display significantly different beta/alpha ratios (t value of 5.41). It is also apparent that 22 per cent of the total sample population can be correctly classified with absolute confidence when beta/alpha ratios fall below 1.54 (normal persons) and above 4.72 (abnormal persons). On an 80 per cent confidence level, 65 per cent of the entire population can be satisfactorily classified, particularly when the observed beta/alpha ratio is below 2.00 or greater than 2.62. Within this confidence limit, therefore, only a relatively small portion of any random population may be expected to fall within the doubtful range.

Beta/Lipalbumin Ratio

The qualitative character of the lipoprotein pattern prepared by our method of electrophoresis reveals that the alpha lipoproteins represent a minor portion of the lipoprotein pattern and, therefore, can be expected to make a small contribution to the foregoing beta/alpha ratio. The lipalbumin fraction, on the other hand, represents a larger physical share of the pattern and plays a greater determinant role in the calculation of this ratio. We have examined, therefore, our data with respect to the usefulness of the beta/lipalbumin ratio in our sample population (figure 12). This index displays a high degree of reliability (t = 4.65) for the separation of "normal" and abnormal groups. In addition it will be noted that the atherosclerotic status of one third of our population can be correctly classified without chance of error, when this variable is below 2.56 or greater than 6.82. On the other hand, if an 80 per cent level of confidence is acceptable, more than half of the population can be diagnosed when values are less than 2.97 or more than 5.12 (table 1).

Discussion

It is commonly accepted that an abnormality in lipid metabolism is intimately associated with the pathogenesis of atherosclerosis.[19, 20] Knowledge of the particular lipids involved or of a precise mechanism is still lacking. In fact, it would appear that this and even the entire subject of atherogenesis and the significance of various proposed laboratory diagnostic procedures for its detection have arrived at a contentious level.[21, 22]

Numerous measurements of serum lipids as

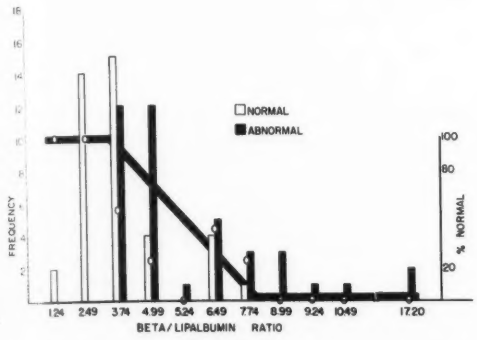

Figure 12

Frequency distribution of beta/lipalbumin ratios in patients with manifest coronary artery disease and controls. Line graph represents the per cent of normal individuals at each level of values.

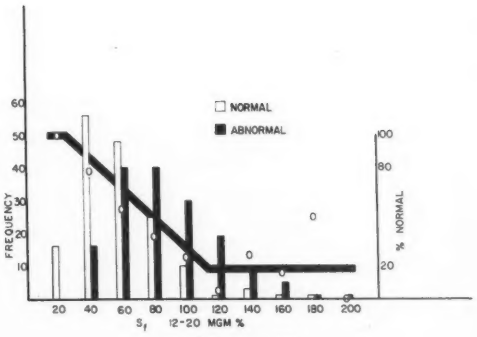

Figure 13

Frequency distribution of Sf 12-20 lipoproteins in an abnormal and control population (data translated from Gofman et al.[22] Line graph represents the per cent of normal individuals at each concentration level.

diagnostic of atherosclerosis have been suggested, namely; cholesterol,[23-26] phospholipids,[20, 23, 25, 27] cholesterol/phospholipid ratio,[25] cholesterol-uric acid/phospholipid ratio,[28] total lipids,[24] neutral fats,[29] saturated and unsaturated fatty acids,[29] as well as lipoproteins determined by chemical fractionation,[30] ultracentrifugation,[3] and electrophoresis.[17, 27, 31] Unfortunately, the information gained by simple chemical analysis has not been deemed sufficiently significant.[18, 24, 27] Current adherence to cholesterol determinations as an index of atherosclerosis appears to be a compromise decision according to Keys, ". . . partly because there is more information about this than any other relevant item of analysis and partly because we still insist there is no evidence that other recommended analytical items have really significantly different or greater diagnostic or prognostic value.[32, 33] This opinion is shared also by Adlersberg and Sobotka,[20] Clough,[21] and Lawry et al.[34]

In essence, we are in agreement with the foregoing. Our observations, however, indicate that serum cholesterol concentrations can have only an extremely limited diagnostic value. By extrapolation of the curve (figure 1) depicting the proportion of normal individuals at each concentration level, it is apparent that only at the extreme values, below 150 or over 400 mg. per cent does this variable reflect the atherosclerotic status of the individual. These findings are in agreement with those of Wagner and Poindexter[26] as well as Sperry,[35] who stated, "unless the total cholesterol content of serum of a patient is extremely low or high, we can not be certain that the amount found is abnormal for that person." Therefore, a manifest weakness of this determination is revealed by the fact that an overwhelming majority of a random population may be expected to fall within the nonsignificant range.

Although phospholipids may play an important role in the solubility of cholesterol and other lipids, from our data at least, their serum concentration per se has no significance in revealing the atherosclerotic status of either the individual or groups. Contrariwise, it may be concluded that the extremely low Fisher t value which we have observed tends to establish an identity between normal and atherosclerotic subjects with respect to this lipid component. In a sense this is not surprising, since the concentration of phospholipids roughly parallels that of total lipids in the blood, an observation supported by a high coefficient of correlation ($r = 0.91$).

The cholesterol/phospholipid ratio appears to be a function of the change in the serum cholesterol level,[20] which is demonstrated by the similarity in the continuous curves shown

in figures 1 and 3. Except for an occasional reference to the contrary,[36] the cholesterol/phospholipid ratio, according to most investigators,[25, 32] bears no relationship to the presence or absence of atherosclerosis. Our own findings show a low level of significance for separating groups and for predicting the status of an individual. By the same reasoning as in the case of cholesterol, the cholesterol/phospholipid ratios may be expected to provide a useful index only at extremely high or low values. Such extreme values, however, are not likely to appear, especially since our data show these variables to have a high coefficient of correlation ($r = 0.84$). This interrelationship has been reported also by others.[25, 32, 37]

It will be noted that total lipid measurements provide a poor index for establishing differences both between normal and atherosclerotic groups and with respect to identifying individuals, since this variable shows zero reliablity at every level of concentration. This presumably is related closely to the dietary habits of the individual.

Lipoprotein analyses by paper electrophoresis have yielded considerable variation in results reported by different laboratories.[9, 18, 31] This variation is confirmed by our experiences with the technics used by those investigators. With our method of electrophoresis but using Durrum's staining procedure,[38] we can routinely demonstrate up to 4 lipid zones. From approximately 200 such Oil Red O-stained patterns, quantitated by our procedure previously described,[10] we have found normal, doubtful, and abnormal beta/alpha lipoprotein ratios ranging from 1.0 to 4.0, 4.0 to 6.0, and 6.0 to 12.0, respectively. This observation has been confirmed more recently by 32 normal and 27 atherosclerotic patients in the present series and 20 tuberculous patients (part of another study), in which Oil Red O and Fat Red 7B lipoprotein patterns were run simultaneously. The relatively greater scatter and poorer reproducibility of the Oil Red O values appear to be the result of the deep coloration of the paper background, which, in turn, produces even lower density readings for those lipoproteins present in low concentration, namely, the alpha and lipalbumin fractions. Undoubtedly other factors such as variations in color hue of stained patterns, even when using a single batch of Oil Red O, also contribute to the variability that we find when using this dye.

By our present technic of lipoprotein staining, 5 lipid zones are consistently demonstrated that are found to coincide with their respective protein fractions. The beta lipoprotein and the gamma plus neutral fat fraction, the "O" zone of Adlersberg, have been described repeatedly in the literature.[7, 17, 18, 38] Our demonstration of an alpha-2 lipoprotein is confirmed by the previous observations of Kunkel and Trautman,[39] Moinat et al.,[40] and Ackerman et al.[41] The presence of an alpha-1, as well as an alpha-2 lipoprotein and lipalbumin such as we find, also has been described by DeGennes and Polonovski.[42] As early as 1941, Blix et al.[43] have claimed that each of the protein fractions contains some lipids. More recently Eiber et al.[44] have shown that ultracentrifugal pretreatment of serum produces a significant reduction in peaks of beta, alpha-2, and gamma globulin as observed in moving boundary electrophoresis. The conclusion that lipids exist in association with all the protein fractions of the serum is inescapable. The alpha lipoproteins generally referred to in the literature, however, represent a combination of all lipoproteins with mobility greater than that of the beta fraction.

All lipoproteins fractionated by paper electrophoresis, except the gamma lipoprotein plus neutral fat fraction, reveal considerably more significant information relative to atherosclerosis than any of the chemical studies. Of these, the beta lipoproteins, lipalbumin, the beta/alpha ratio and the beta/lipalbumin ratio appear to offer indices that make it possible to classify correctly a large percentage of individuals in our sample. For example, our data dealing with the lipalbumin fraction alone enable one to distinguish the normal from the abnormal group with an exceedingly high degree of confidence ($t = 5.8$) and it is also possible to diagnose one third of the pop-

ulation individually with absolute certainty. Better than one half of the population can be classified individually if an 80 per cent level of confidence is acceptable.

In view of the low relative concentrations of the alpha-1 and alpha-2 lipoproteins we think that they play a rather minor role in transport and metabolism of lipids. On the other hand, our data would support the idea that lipalbumin is considerably more important in the handling of blood lipids than either of these. This view is also indirectly borne out by the fact that the hyperlipemia associated with nephrosis essentially is the result of a hypoalbuminemia.[45] It may be inferred thereby that the lipalbumin fraction may have greater significance in reflecting lipid metabolism than was previously appreciated.

In our considerations of the beta/alpha ratio, we have followed the established precedent in calculation. For example, Kanabrocki et al.[18] and Adlersberg et al.[17] calculate beta/alpha ratios by excluding the gamma and neutral fat fraction and dividing the beta lipoprotein fraction by the balance of the lipidophilic material. With this method of calculation the difference in mean values between normal and abnormal groups in our study is highly significant ($t = 5.41$). We have found the beta/alpha ratio to be highly correlative with the atherosclerotic status of the individual, since 65 per cent of the total sample population can be classified on an 80 per cent confidence level with values falling below 2.00 and above 2.62. Similar conclusions can be drawn from our data in terms of beta/lipalbumin ratios.

Of the 5 lipoprotein fractions that we have examined, only 2, the beta lipoprotein and the lipalbumin, provide the most useful data, which is not surprising, since these fractions are present in largest concentration and may be presumed to play dominant roles in lipid metabolism. Our data would appear to be considerably more useful than those reported by Jencks et al.,[31] who, while claiming that lipoprotein electrophoretic patterns distinguish groups of normal controls from patients with myocardial infarcts, show scatter diagrams in which the degree of overlap between these 2 groups reveals that it is impossible to distinguish more than a very small fraction of the population on an individual basis.

In order to compare Gofman's atherogenic index with ours we have replotted Gofman's data[22] concerned with Sf 12-20 lipoproteins (fig. 13). Remarkably similar trends are noted between Gofman's index and our beta/alpha ratios (fig. 11) but more detailed analysis is not possible without the original data.

Unquestionably an area of overlapping values exists in all such determinations. This can be accounted for by our inability to separate adequately the symptomless atherosclerotic individual from the true normal. In addition, this area of doubt is also contributed to by a considerable number of individuals who, having displayed evidence of coronary artery disease, spontaneously or through medical management, may have adjusted their lipid metabolism so as to interrupt the phenomenon of atherogenesis. This type of course would suggest, therefore, that the pathogenesis of the disease may not be a continuous but rather an intermittent process, and in a sense holds promise for its eventual management. The myocardial infarction, the coronary insufficiency, and the thrombosis are the result of the coronary atherosclerosis, which itself is a secondary manifestation of an underlying metabolic disease. An abnormal atherogenic index in terms of lipoproteins, therefore, must be construed to imply the developing phase of the disease of the arterial wall per se, and not necessarily the extent to which it exists at the time of sampling.

The data thus far discussed appear to warrant further investigation to include a larger population, which is currently in process.

Summary

Data dealing with cholesterol, phospholipid, their ratios, and total lipids in a group of 40 "normal" and 40 individuals with manifest coronary artery disease have been evaluated and have been found to have a low order of significance in determining the atherosclerotic

status for both individuals and for groups.

Serum lipoproteins separated by paper electrophoresis and visualized with Fat Red 7B have been shown to occur in 5 fractions. Of these, lipalbumin and beta lipoproteins as well as beta/alpha and beta/lipalbumin ratios reveal a high level of significance for distinguishing normal from abnormal individuals and groups.

Acknowledgment

The authors wish to acknowledge the technical assistance of Mrs. Marylin Kattan and Miss Shirilyn Shulman.

Summario in Interlingua

Datos relative a cholesterol, phospholipido, le proportion inter le duo, e lipido total, esseva evalutate in 40 subjectos normal e in 40 con manifeste morbo de arteria coronari. Esseva trovate que ille datos es pauco significative in determinar le stato atherosclerotic tanto de individuos como etiam de gruppos.

Esseva monstrate que le lipoproteinas del sero, quando separate per electrophorese a papiro e visualisate con rubio grasse 7B, occurre in 5 fractiones. Inter istos, le valores pro lipalbumina e le lipoproteinas beta e pro le proportiones beta a alpha e beta a lipalbumina revela un alte grado de signification in le differentiation inter individuos e gruppos normal e anormal.

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Myocardial Infarction in Patients Treated with Sippy and Other High-Milk Diets

An Autopsy Study of Fifteen Hospitals in the U.S.A. and Great Britain

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IT HAS been reported that the incidence of myocardial infarcts is higher among persons with chronic peptic ulcers than among others.[1, 2] This higher incidence may be due to the type of diet consumed by these patients. Milk products are suspect because of their common use by ulcer patients. Butter fat is particularly suspect because it has an effect on blood coagulation[3] and clot lysis,[4] because it is a major constituent of diets that produce coronary thrombosis and myocardial infarcts in experimental animals,[5] and because of its effect on blood cholesterol levels in man under certain conditions.[6]

It occurred to us that we might obtain important information by dividing patients with chronic peptic ulcer who had come to autopsy into 2 groups: (1) those whose treatment included the use of milk or cream (such as the Sippy diet), and (2) those whose histories did not indicate that their therapy included the use of milk or cream. If the patients who consumed milk or cream as part of their therapy had a higher incidence of myocardial infarcts than those who had not been given this type of therapy, it would at least suggest that the higher incidence of infarcts was related to the therapy. Such an association would not constitute absolute proof of the relation of consumption of milk and cream to the higher incidence of myocardial infarcts in patients with peptic ulcer, since some unknown factor of selection may enter into the choice of patients to be placed on a diet including milk or cream; some other part of the therapy might play a role.

It seemed to us that the best way to minimize factors of selection would be to study autopsies of patients from many different medical centers and therefore probably treated for their peptic ulcers in many different ways. Also, by studying autopsies from various places, we could obtain a larger number of autopsies for analysis than would be available from a single institution, and it would be possible to use more rigid criteria in matching groups for comparison. It seemed important to match groups of patients by age, sex, race, and place and period of death.

Therefore, we have carried out a study of the incidence of myocardial infarcts among 3 matched groups of autopsied patients from 10 centers in various parts of the United States and in 5 centers in Great Britain. The groups are (1) patients with peptic ulcers of the stomach or duodenum found at autopsy who gave a history of having been treated with a Sippy diet or its equivalent (Sippy ulcer), (2) patients with a peptic ulcer found at autopsy who did not have a history of such dietary therapy (non-Sippy-ulcer), and (3) patients without ulcers chosen to match each patient of each of the above 2 groups by taking the next autopsy performed on a patient of the same age, sex, and race (non-ulcer). Patients with acute peptic ulcers were not included in the study because most of them would not have a history of dietary therapy. The pathologic diagnosis was used as the criterion of chronicity of an ulcer when it was definite; otherwise a microscopic description of fibrosis at the base of the ulcer was required before the ulcer was tabulated as "chronic."

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Supported by funds provided by the National Dairy Council. Dr. Zoe Anderson of the National Dairy Council suggested this study.

Mr. Briggs and Mr. Rubenberg were recipients of Summer Research Fellowships from Washington University at the time of the study.

The purpose of this report is to present the results of the study regarding the incidence of myocardial infarcts in the various groups. Both acute and healed myocardial infarcts were tabulated to determine the incidence of myocardial infarcts. The pathologic diagnosis on the autopsy protocol was accepted for the purposes of this study, and such diagnoses as "focal fibrosis" were not tabulated as infarcts.

Material and Methods

Clinical and autopsy records for the years 1940 to 1959 were examined from the following hospitals in the U.S.A.: Barnes Hospital, St. Louis; Massachusetts General Hospital, Boston; Charity Hospital of Louisiana, New Orleans; University of California, San Francisco; Western Reserve University, Cleveland; University of Illinois, Chicago; Johns Hopkins Hospital, Baltimore; Mt. Sinai Hospital, New York; Boston City Hospital, Boston; Cook County Hospital, Chicago.

The data recorded included site of chronic peptic ulcer, age, sex, race, year of death, height, body weight, history and duration of diabetes, history and duration of therapy with "Sippy" diet or similar diets including milk products, principal diseases at death, and presence or absence of a myocardial infarct, with the description of the anatomic characteristics of the infarcts as given in the autopsy protocol.

Each ulcer patient was matched with the nearest non-ulcer patient in the autopsy records of the same age (decade of life), race, hospital, and period of death (± 5 years). The data from the non-ulcer control were attached permanently to the data from its ulcer mate.

After the survey was completed, the records were accumulated from all hospitals and divided into a Sippy-ulcer group and a non-Sippy-ulcer group. Patients in these 2 groups were matched by age, sex, race, hospital, and period of death. Since the non-ulcer control for each patient in the above groups remained attached, 3 groups matched for the above characteristics were thus available. Cases that could not be matched were discarded from the study.

After the matching was complete, the incidence of myocardial infarcts and other characteristics were tabulated for each of the 3 groups (tables 1 and 2).

A study identical in design to the one in the U.S.A. was carried out in the following British hospitals: Bristol Royal Infirmary, Bristol; Western Infirmary, Glasgow; Royal Victorian Infirmary, Newcastle-on-Tyne; St. Mary's Hospital, London; and the British Postgraduate Medical School at Hammersmith Hospital, London. Although the Sippy diet per se is used infrequently in Britain, patients with a history of increased intake of milk for treatment of an ulcer were placed in the Sippy-ulcer group. Milk and alkali powders constitute a common form of treatment for ulcers in Britain.

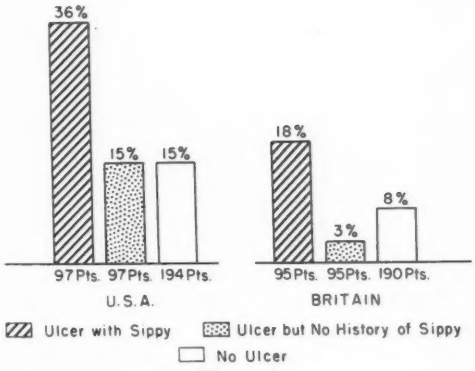

Figure 1

Incidence of myocardial infarcts among patients on Sippy or other high-milk diet compared with controls matched for age, sex, race, hospital, and year of death.

Results

The results are presented in tables 1 and 2 and in figure 1. It is apparent from table 1 that the average heights and weights differ little for the 3 groups. The incidence of diabetes mellitus was too low in all groups to be of importance. Removal of all diabetic patients from the study does not significantly alter the results. Deaths of the patients were due primarily to complications of the ulcer in 34 of the Sippy-ulcer patients and 23 of the non-Sippy-ulcer patients.

The incidence of myocardial infarcts (table 2) among the ulcer patients in the United States not treated with the Sippy diet is identical with that in the non-ulcer group (15 per cent). The 36 per cent incidence of myocardial infarcts in the ulcer groups treated with the Sippy diet is significantly higher than that in the other 2 groups ($p<0.01$). If the 21 patients who had been on the Sippy diet for a year or less are eliminated, the incidence of myocardial infarcts rises to 42 per cent.

Table 1

Some Characteristics of Three Matched Groups of Autopsied Patients

	U.S.A. (average age—60 ± 10)		
	Sippy-ulcer	Non-Sippy-ulcer	Non-ulcer
Average height (cm.) with standard deviation	168 ± 8	166 ± 11	167 ± 10
Average weight (Kg.) with standard deviation	67 ± 16	64 ± 13	67 ± 18
History of diabetes	1 patient	3 patients	6 patients
Diabetic subjects with myocardial infarcts	1 patient	2 patients	4 patients

	Great Britain (average age—59 ± 11)		
	Sippy-ulcer	Non-Sippy-ulcer	Non-ulcer
Average height (cm.) with standard deviation	171 ± 8	173 ± 8	171 ± 10
Average weight (cm.) with standard deviation	57 ± 12	55 ± 12	59 ± 15
History of diabetes	3 patients	3 patients	7 patients
Diabetic subjects with myocardial infarcts	none	none	none

Table 2

Incidence of Myocardial Infarcts among the Three Groups of Patients

	U. S. A.		
	Sippy-ulcer*	Non-Sippy-ulcer	Non-ulcer
No. of cases	97 (85M, 12F)†	97 (85M, 12F)	194 (170M, 24F)
No. with myocardial infarcts	35	15	30
% with myocardial infarcts	36	15	15

	Great Britain		
	Sippy-ulcer‡	Non-Sippy-ulcer	Non-ulcer
No. of cases	95 (74M, 21F)	95 (74M, 21F)	190 (148M, 42F)
No. with myocardial infarcts	17	3	16
% with myocardial infarcts	18	3	8

*If the 21 patients in this group who had been on the Sippy diet for only 1 year or less (average age of these 21 patients was 62 years) are eliminated, the percentage of infarcts in the 76 remaining patients rises to 42 per cent. Many of these 76 had been on the Sippy diet for over 10 years.

†The number of patients of each sex is given here for easy reference.

‡In this group of British patients only 11 patients' diets were actually called "Sippy," and 3 of these 11 patients had infarcts. However, all patients in the Sippy-ulcer group had a history of therapy with milk.

The incidence of myocardial infarcts (table 2) among the ulcer patients in Great Britain with a history of treatment with milk was 18 per cent, significantly higher ($p<0.01$) than the 3 per cent incidence in the non-Sippy-ulcer group and the 8 per cent incidence in the non-ulcer controls ($p<0.05$). The difference in incidence between the latter 2 groups is not statistically significant.

Discussion

The results of this study show clearly that there is a much higher incidence of myocardial infarcts among autopsied individuals with peptic ulcers who have been treated with the Sippy or similar diets than among ulcer patients not treated in this way or among non-ulcer controls. This association might indicate some conscious or unconscious factors of selection in determining which patients should be placed on the Sippy regimen. However, it seems unlikely that this is the real explanation. In some of the centers the Sippy diet was used commonly but in others very seldom, suggesting that its use is influenced by local therapeutic philosophies and backgrounds.

A more likely explanation is that something

in the diet associated with medication increases the incidence of infarcts. One possibility is that it has something to do with antacids such as the commonly used aluminum hydroxide or magnesium trisilicate. There is no evidence at present that they have anything to do with myocardial infarction.

Another possibility is that the dairy products that form a prominent part of the diet are responsible. Considerable experimental evidence has been reported that butter has an effect on blood coagulation and clot lysis in man and animals;[3, 4, 7, 8] also, a diet containing a large proportion of saturated fat such as is found in butter tends to increase the cholesterol level in the blood over the levels obtained with certain other fats.[6] In addition, arterial thrombi and myocardial infarcts have been produced in large numbers of rats given diets containing, among other ingredients, large quantities of butter.[5, 9]

Even if the increased intake of milk is responsible for the high incidence of myocardial infarction in ulcer patients, the identity of the specific constituent of milk that is important in this respect has not yet been established. The mineral component of milk, for example, may be as important as the fat content.

Although at present the butter-fat content of the Sippy diet would seem to be the most likely culprit, it must be emphasized that proof beyond reasonable doubt has not yet been presented in this study. The association certainly warrants suspicion, but it does not constitute proof. Further investigation will be necessary, such as studies of coagulation, fibrinolysis, and cholesterol levels in the blood of living patients with peptic ulcers who are being treated with and without the use of milk products.

An incidental observation of the present study was a lower incidence of myocardial infarcts among the patients in England than in comparable groups in the U.S.A. This is consistent with the results of other studies of clinical and autopsy material, as well as vital statistics.[10, 11] The incidence of myocardial infarcts among the Sippy-ulcer patients in England, although much higher than in the British non-ulcer controls, was essentially the same as the incidence in the non-ulcer controls in the U.S.A. This could be interpreted as evidence that the comparatively high incidence of myocardial infarcts in the control groups in the U.S.A. might be due to the high over-all consumption of milk products, but there are too many uncontrolled variables for this interpretation to be warranted.

The patients in the U.S.A. weighed an average of 8 to 10 Kg. more than the British patients and were a few centimeters shorter. The difference in height may be due to different technics of measurement; in Great Britain the measurement in some hospitals is taken from the ball of the foot instead of the heel.[12] In both the American and British groups, the Sippy-ulcer patients who had a high incidence of infarcts weighed no more than the non-ulcer controls with a low incidence of myocardial infarcts.

Diabetes mellitus is a well-known factor in the production of myocardial infarcts. In this study elimination of the patients with a history of diabetes did not significantly alter the results.

It occurred to us that the severity of the ulcers might be different in the patients treated with Sippy diet and the non-Sippy-ulcer patients. In the patients in the U.S.A., 38 of the patients on the Sippy diet and 23 of the ulcer patients not on the Sippy diet died of complications of the ulcer, either hemorrhage, perforation, obstruction, or following operation. This would appear to indicate that, in general, the patients on the Sippy diet had a somewhat more severe disease than those not treated with the Sippy regimen, but we are unable to see how this difference would alter the interpretation of our results.

Summary

A study has been made of the incidence of myocardial infarcts among 3 groups of autopsied patients who were matched for age, sex, race, and place and period of death: (1) patients with peptic ulcers who had been treated with a Sippy diet or milk products,

(2) patients with peptic ulcers who were not known to have been so treated, (3) a group consisting of non-ulcer patients matched with the other 2 groups.

In the U.S.A. the incidence of myocardial infarcts was more than twice as high in the ulcer patients treated with Sippy diet than it was in either of the other 2 groups. The differences in each case were statistically highly significant. There was no significant difference in the incidence of myocardial infarcts between the ulcer patients not treated with the Sippy diet and the non-ulcer controls.

Differences and similarities of the same degree were noted among corresponding groups from Great Britain. It is tempting to think that the high incidence of myocardial infarcts among the Sippy-treated patients was a result of the butter-fat content of their diets. Mere association, however, does not constitute proof and further study is needed before definitive conclusions are drawn.

Acknowledgment

We wish to thank the hospital authorities, and particularly the pathologists at the various hospitals visited, for their kindness in allowing us to use their material.

Summario in Interlingua

Esseva effectuate un studio del incidentia de infarcimento myocardial in tres gruppos de necropsiate patientes qui esseva comparabile ab le punctos de vista del etate, del sexo, del racia, e del placia e del tempore de lor morte. Le tres gruppos esseva (1) patientes con ulceres peptic qui habeva essite tractate con le dieta de Sippy o un altere dieta de productos de lacte, (2) patientes con ulceres peptic qui non habeva cognoscitemente recipite un tal tractamento, e (3) un gruppo de patientes sin ulceres.

In le Statos Unite le incidentia de infarcimento myocardial esseva plus que duo vices plus alte in le patientes tractate con le dieta de Sippy que in tanto le un como etiam le altere del 2 gruppos sin ille tractamento. In ambe casos, le differentia esseva statisticamente significativissime. Il non existeva un differentia significative in le incidentia de infarcimento myocardial inter le patientes con ulcere non tractate con le dieta de Sippy e le patientes de controlo sin ulcere.

Differentias e similitudes del mesme grados esseva notate inter correspondente gruppos de patientes in Grande Britannia. Es seductive le notion que le alte incidentia de infarcimentos myocardial inter le patientes tractate secundo Sippy esseva le resultato del alte contento de grassia butyric in lor dietas. Tamen, un simple association non es un prova de un interrelation causal, e studios additional es requirite ante que conclusiones definitive pote esser formulate.

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Transient Complete Heart Block Occurring during Nasal Irrigation

By GERALD M. MURPHY, M.D., J. G. WILMER, M.D., AND T. S. CLAIBORNE, M.D.

CARDIAC standstill and sudden death have been reported in operative procedures of the eyes, ears, nose, and throat and in intubation procedures.[1-3] The exact mechanism and cause of these episodes are not entirely clear. The question of vagal effect with inhibition of the heart beat has been considered as a factor. The present case is reported because of the possibility of cardiac inhibition by vagal reflex. The stimulating factor in this patient was a high pressure spray of isotonic saline solution in the area of the sphenoid sinuses.

Case Report

The patient was a 54-year-old white woman who was admitted to St. Joseph's Infirmary in collapse on February 3, 1959. In her past history there was a rather marked psychoneurotic background after a surgical menopause in 1930. The chief symptom was headache, which had been related on occasion to sinusitis requiring frequent local treatments. Another symptom was substernal pain not typical of, but considered to be consistent with coronary artery insufficiency. This view was supported by minor electrocardiographic changes (fig. 1*A*) in January 1959.

On February 3, 1959, the patient collapsed in the chair of an otolaryngologist while receiving a forceful jet spray of isotonic saline solution into the area of the sphenoid sinus. She quickly became cyanotic and lost consciousness. She was placed in the recumbent position, and oxygen was administered by catheter orally. When examined 5 minutes later, she was unconscious, ashen, perspiring profusely, and had slow gasping respirations. The neck veins were distended but the lungs were clear. The blood pressure was unobtainable, and the pulse was faint and extremely slow. The heart beat was regular, with a rate of 32. During examination she had a brief major convulsion. Epinephrine 1:1000, 0.5 ml., and 1 mg. of atropine were given intramuscularly. An electrocardiogram showed an idioventricular rhythm and atrial fibrillary waves (fig. 1*B*). Over a period of 15 minutes her condition improved although the electrocardiogram remained unchanged. She was then transferred to the hospital by ambulance about 45 minutes after the onset of trouble. She was unconscious at this time, and oxygen was administered during the transfer by a Boothby mask.

On admission to the hospital she was placed in an oxygen tent and a dilute solution of norepinephrine (Levophed) was started intravenously, even though her pulse was about 70 on admission and her blood pressure was 112/84. She gradually regained consciousness, and 2 hours later the blood pressure was 125/85, and the pulse was 74. With this improvement Levophed was discontinued after the administration of only 20 ml. At this time weakness of the left hand, slurring of speech, and bilateral Babinski reflexes were observed. The situation seemed to be one of acute myocardial and cerebral anoxia, with the inciting episode uncertain. However, 12 hours later the electrocardiogram (fig. 1*C*) reverted to the same pattern as before the episode. The blood pressure and pulse were normal and the patient was comfortable except for minor precordial distress; but she still had weakness of the left hand, a Babinski reflex on the left, and her reactions were slowed. Evidence of myocardial damage was demonstrated by elevation of the serum transaminase (100 units on admission and 76 units on the seventh day), and by the development of T-wave changes (fig. 1*D*) on the fourth day, indicating inferior myocardial involvement. Blood electrolyte studies and routine blood examinations were normal, except for an admission white count of 12,600.

The patient was discharged after 2 weeks in the hospital and within 2 months had returned to normal activity. There has been no evidence of further cardiac difficulty and the electrocardiographic pattern (fig. 1*E*) returned to that taken prior to the episode. From the neurologic standpoint there remained only slight clumsiness of movements of the left hand.

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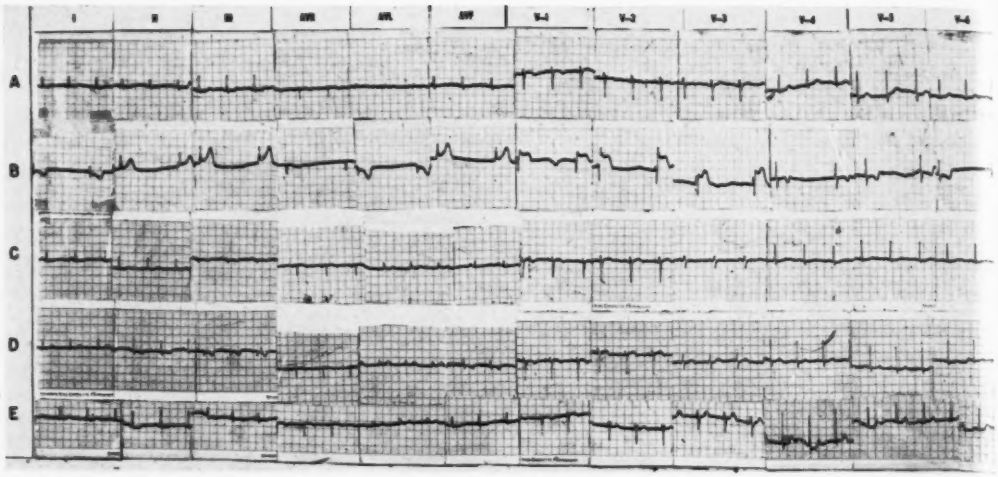

Figure 1

Electrocardiographic tracings in patient before, during, and after nasal irrigation. A. *Tracing taken in January 1959.* B. *Tracing during period of collapse, showing idioventricular rhythm and atrial fibrillation.* C. *Reversion to previous pattern.* D. *Tracing taken on February 7, 1959, indicating posterior myocardial infarct.* E. *Tracing taken 2 months later, similar to that in* A.

Discussion

Clinically, this patient developed a sudden arrhythmia, probably a period of cardiac standstill followed by complete heart block, during a nasal procedure, and developed cerebral and myocardial anoxia and necrosis during the resultant period of decreased blood flow. The initiating factor in this arrhythmia is thought to be a vagovagal or trigeminovagal reflex. A myocardial infarct occurring about the time of the nasal irrigation could have produced a sudden arrhythmia, but such a possibility seems remote.

The vagal reflexes are mechanisms of great importance, and are often a factor in the production of cardiac arrest. Reid and associates[4, 5] described "the reflex nature of the derangements in cardiac dynamics following mechanical irritation of the mucosa of the respiratory or gastro-intestinal tracts by a wide variety of contrivances, such as intratracheal tubes and catheters, bronchoscopes, gastroscopes, esophagoscopes, inflation of cuffs, etc., or even spraying of the throat with water." He described a child who developed cardiac arrest during adenoidectomy, and developed further episodes of arrest during removal of adenoidal packs the next day. Further manipulation was deferred until the administration of atropine, following which the packs were removed without incident. Weiss and Ferris[6] described a patient with an esophageal diverticulum who experienced brief episodes of complete heart block with unconsciousness after swallowing. Similar attacks could be induced by inflating a balloon in the diverticulum, and they were abolished by atropine.

The vagovagal reflex is initiated by stimulation of the afferent endings of the vagus, which are widely scattered through the carotid sinus and the gastrointestinal and respiratory tracts, including the trachea and pharynx. In some instances the pathway of the reflex is to the vagal center in the medulla, and hence over the efferent fibers; in others the impulse travels by an axon reflex directly from afferent to efferent fibers of the vagus without reaching the brain. In what might be termed the "trigemino-vagal" reflex the impulse arises in the region of the eye, upper nasopharynx, or nasal sinuses and is trans-

mitted through the trigeminal nerve to the brain, and hence to the vagal center and efferent pathway. This reflex is responsible for the effect of ocular pressure on paroxysmal atrial tachycardia, and occasionally for cardiac arrest during eye surgery. The exact point of stimulus in our case would be uncertain, but it was probably within the trigeminal sensory distribution.

The efferent vagal fibers are scattered throughout the atria, but are not found in the mammalian ventricle. Vagal stimulation reduces the rate of impulse formation in the sinoatrial node and may cause atrial arrest; also there may be delayed conduction through the atrioventricular node resulting in heart block of various degrees, from a slightly increased P-R interval to complete heart block. In a normal myocardium vagal atrial arrest is followed by the development of an idioventricular rhythm capable of maintaining circulation, but in a myocardium depressed by an anesthetic agent, anoxia, or preexisting disease, an adequate ventricular rhythm may not be initiated.

In the present case it is difficult to trace the sequence of events immediately after the vagal stimulation. Tracing (fig. 1*B*) taken 20 minutes later, during the period of unconsciousness, shows atrial fibrillary waves, and ventricular complexes generally similar to those of the control tracing, with a rate of 46 to 54. At first appearance, the tracing suggests atrial fibrillation, with a high degree of atrioventricular block, such as might occur from digitalis or vagal stimulation from carotid sinus pressure. However, with the regular ventricular rhythm and extremely slow ventricular rate (32) when the patient was first seen, it would seem more likely that there is complete block with the ventricular impulse arising near the atrioventricular node. Although it seems likely that the vagal reflex precipitated the block, the preexisting coronary disease may have been a factor in this and in the subsequent myocardial damage.

Episodes of cardiac arrest and rhythm changes during operative procedures and intubation occur with such rapidity that observations as to the mechanism of the arrhythmia are difficult to obtain. Atropine abolishes the vagal reflex and is widely used preoperatively and the relation of the use of this drug to such episodes should be carefully determined.

Summary

Cardiac standstill associated with surgical work about the eyes, nose, and throat occurs but is not frequent.

A case is reported in which the patient collapsed while receiving a treatment with a jet spray in the sphenoid sinus area. There developed heart block and cerebral and myocardial damage. Vagal stimulation with inhibition of the heart beat is suggested as the probable cause.

Summario in Interlingua

Arresto cardiac in association con manipulationes chirurgic in le area del oculos, del naso, e del gurgite pote occurrer sed non es frequente.

Es reportate un caso in que le patiente collabeva durante que le area de su sinus sphenoide esseva tractate con un jecto irrigatori. Superveniva bloco cardiac e damno cerebral e myocardial. Es opinate que le causa probabile esseva stimulation vagal con inhibition del pulso cardiac.

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SPECIAL ARTICLE

Social Aspects of Cardiovascular Rehabilitation

By MARVIN C. BECKER, M.D., WAYNE VASEY, M.A.,
AND JEROME G. KAUFMAN, M.D.

THE enormity of the problem of heart disease with its physical implications is well known, but its effect on the socioeconomic structure of the family, community, and government is not realized by all in the medical profession. That heart disease is the leading cause of death;[1] that 5 per cent of working people are afflicted;[1] that 400,000 people with coronary artery disease are being added to the labor market yearly;[2] that it exacts its heaviest toll from those with the greatest responsibility over 40 years of age[3] are readily appreciated facts. That 653,000 man-years are lost each year as a result of cardiovascular disease and that this loss was equivalent to $2,468,340,000 in earnings alone in 1953,[1] are but a few of the statistics that one reads frequently and might readily comprehend. But the social implications are not widely understood nor are the resources of combating the problem a matter of common knowledge.

What do all these staggering statistics signify? They mean that a progressively larger number of people will be dependent upon their families and governmental aid, unless they can support themselves. Experience with the disabled cardiac patient indicates more and more the importance of collaboration between the physician and other helping disciplines. The spectrum of rehabilitation with its physical, emotional, economic, and social components includes a range of skills outside the competence of any one discipline. Coordinated efforts of the physician, social worker, nurse, rehabilitation counsellor, occupational therapist, physical therapist, and the employment service may be engaged in whole or in part on behalf of the patient. Community resources to provide these services present pictures of varying degrees of adequacy. Adequate or not, however, they should be known and utilized by the physician.

It is our purpose to point up the social factors determining the high incidence of disability among cardiac subjects and to underscore what resources may be recruited to diminish this incidence.

Social Factors Determining the High Incidence of Disability

Rehabilitation of the disabled cardiac would not be such a great problem if the physical incapacity of the patient were the only factor to be solved. Great strides have been made in this field, and numerous studies have demonstrated that the cardiac can work, does work, that work is not harmful, that work may be beneficial, that absenteeism is rare, and that there is little risk in hiring the cardiac patient. In spite of these advances in knowledge, there are, unfortunately, many potent forces involved in the high incidence of disability.

Character of the Patient's Work and Skills

The character of the patient's work and training has many facets. One must consider these forces when matching the patient's ability against the stress of the job. Although it is recognized that a great deal of progress has been made by physiologists in assessing the energy requirement of the work, many intangible and unmeasurable factors must be considered. The overdemanding employer or foreman may complicate what normally may have been a suitable job. Competitive piece-

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work may also increase physical and emotional demands. Whereas job stress and physical ability may seem to harmonize, at times, failure may be met by prolonged and difficult modes of travel to and from work. Often the method of travel requires more energy than the work itself.

The patient's skills—or lack of skills—add to the incidence of disability. There is no question that the skilled indispensable worker has a greater chance for rehabilitation than the one lacking in such attributes. He has more to offer, usually with less energy requirement. The laborer, especially the older one, who must depend upon his brawn for a livelihood, may be hard put to find a job when disabled by a cardiac condition. He has little to offer except strength, and this has often ebbed. For example, a miner with a coronary occlusion might be totally disabled, whereas a watchmaker, jeweler, accountant, typist, and others in such light work categories might have no disability whatsoever.

The patient who is self employed is in an enviable position. He might work less, be willing to live on less, receive long deserved help from his highly indulged family; he might hire additional employees and get along admirably. It is interesting to note in this respect that 90 per cent of the self employed return to work.[4]

The Physician

It is unfortunate that the physician must be indicted at times as an important social force in the cause of cardiac disability. In general, he may abuse the time-honored concept of rest, forgetting that too much rest when used injudiciously may lead to physical and emotional incapacity.[5] Rest and inactivity, once a cardiac lesion has healed, does not prolong life. One thing is certain; it may lead to bitterness and unhappiness for the patient and those surrounding him.

The physician, also is subject to social and economic pressures. He may unwittingly be reassuring in order to protect himself. He may mention murmurs of a functional nature or slight electrocardiographic changes with no other corroborating evidence of heart disease. He does this, perhaps, in fear that some other physician may discover these abnormalities and thus subject his ability to question. Inadequate training in cardiology also may lead to faulty diagnosis of minor changes and thus produce a train of events with anxiety symptoms and cardiac disability far outweighing the physical state.[6]

Also, because of possible disorderly and indefinite indoctrination in rehabilitation, the physician may be ambiguous in instructions to the patient. This should be avoided. The orders that are given should be specific when possible. The work formula should fit the patient. The phrases "take it easy" and "look for a lighter job" should be discarded from the physician's vocabulary. The insecure physician afraid of censure may place unnecessary restriction on the patient with reference to food, coffee, tea, cigarettes, sex, and other pleasures, thus dramatizing the illness. Although the benefits of such restrictions are questionable, they tend to emphasize the gravity of the ailment to the patient and add to his disability.[7]

Stress of Living

The stress of daily living, with its competition, high cost, conformist attitudes, deadlines, responsibilities, and lightning decisions, is often indicated as an important factor in causing cardiac disability. This, of course, is a popular concept to the physician as well as the layman. It certainly is more admirable to be a victim of diligence and ambition rather than gluttony and inactivity, which is more likely in light of present knowledge. Stress of living per se must be examined in more critical light, and its effect as a cause of disease must await further proof.

Interesting, along this line of thinking was a recent investigation by Lee and Schneider,[8] who made a comparison between 1,171 male executives and 1,203 nonexecutives observed over a period of 5 years with respect to evidence of arteriosclerosis and hypertension. This study was done to confirm or deny the popular conception that executive responsi-

bilities increased the incidence of cardiovascular disease. The results of this study were surprising in that the executives over 40 years of age had no greater incidence of hypertension and a disproportionately low incidence of generalized arteriosclerosis, arteriosclerotic heart disease, and myocardial infarction. This finding, of course, does not rule out the effect of emotional stress because as the authors point out, "stress is a relative matter and the disruption of the harmonious balance between a man and his environment can result from either the demands of the environment or the failure of a man to measure up to them. Success in a career goes hand and hand with good health. The executive, as part of his training, learns to judge the amount of occupational stress he can stand and to appreciate the value of outside avenues of expression."

Whereas the stress of living cannot be indicted as a cause of heart disease, there are certain *external forces* in existence that aggravate preexisting heart disease. These forces may be stimulated by our newspaper and magazine articles, radio and television dramatization of cardiac disease, and advice of well-meaning and misinformed friends. Every sudden death that is highlighted in the press and acted out on television offers little solace to the patient with heart disease and, if anything, intensifies his disability. The overcautious parents of the child with rheumatic heart disease may be cited as the classical example of an anti-rehabilitative force. The overprotective wife and children of the husband and father with coronary or hypertensive heart disease may exert a dynamic influence on the patient. The wife frequently denies him food, alcohol, and sexual gratification. Physical effort and diversions are prohibited in hopes of preventing recurrence. The unstable individual may succumb to this secondary gain and become unproductive.

The Attitude of Industry

Large industries have a definite aversion to employing persons known to have cardiac disease. Olshansky et al.[9] in a review of employment practices in the Boston area indicated that about one half of 100 employers in the survey excluded patients with cardiac disease from new employment. Only 99 known cardiac subjects were hired among 13,431 new employees. The potential risk of Workmen's Compensation costs was given as the primary deterrent to such employment. Other restraining factors were the lack of suitable jobs and the added cost of sickness benefit plans. Lee et al.[10] in another industrial survey noted that only 242 cardiac workers out of 19,321 new employees were hired. Kline[11] in another survey discovered that 71 per cent of industrial physicians were reluctant to hire cardiac patients because they considered that the physical demands of the work exceeded the physical capacity of the cardiac patient. It was noted, however, that employers are prone to continue in employment those workers who develop cardiac disabilities during their employment.

There is a general tendency to condemn industry for its attitude toward cardiac employment. There is also a hope that they should act as rehabilitation centers. In all fairness, however, one should examine the other side of the coin. The fact remains that American industry is highly competitive and must have full efficiency to survive. Unless industry can be convinced that it will receive maximum efficiency from the cardiac patient, it is only natural to assume that there will be unwillingness to hire him. Those in the private practice of medicine also readily appreciate the fact that people are very claim-conscious today. Industry knows this from experience and their fears of liability and higher insurance rates may have justification.

It has been reported that in New York State alone, Workmen's Conpensation payments for heart disease amount to about two million dollars annually.[12] This underscores the severity of the situation and reemphasizes the fact that the fears of the employer have a substantial basis.[13]

Age

The social aspects of aging itself with the relationship to employment are subjects that

m: well be covered in an individual thesis. Sufice it to say for our purposes, however, th the older the cardiac person with disabi y, the less is his chance for employment. In eneral, there is a resistance by employers to ire older people, with or without disability.

Sta us of the Labor Market

The availability of jobs is important. During a recession with high unemployment, the chances of the cardiac person receiving employment are less. It is only natural for the employer to desire maximum efficiency with a minimum of risk. During boom times when industry is thriving and a labor shortage exists, cardiac disabilities might be easily overlooked. The employer is willing to take the added risk. It was shown during World War II, when the able-bodied were in the Armed Forces, that the chance for employment of the cardiac subject was greater.

Abuse of Workmen's Compensation Laws; Old Age, Survivors and Disability Insurance; Temporary Disability Insurance and Pensions; Health and Accident Plans

Social legislation, with all its inherent benefits may be abused. At times, one may feel that it is a deterrent to work. In reading many of the writings on cardiovascular rehabilitation, one gathers a feeling of resentment on the part of the authors toward the value of social legislation. In general, the value of legislation must not be judged by the few that abuse it. The internist or cardiologist must remember that his statistical sampling is poor.

Ironically, at times, this social legislation, especially Workmen's Compensation Laws, does harm to the cardiac patient and prevents his rehabilitation. Because of the costs of the program, the employer may be reluctant to hire a known cardiac patient, or rehire one who had suffered an attack at work. This has been intensified by the recent liberal trend of the courts in the interpretation of the Workmen's Compensation Act. Instead of causal relationship depending upon "an accident arising out of and during the course of employment," recent decisions in many states have depended on the mere act of being employed. This has stemmed from the fact that some upper courts have a tendency to give more weight to a philosophical and emotional concept rather than a consideration of the evidence and scientific medical testimony.

In New Jersey, for example, cases were decided for many years on the "unusual exertion theory," i.e., if the initial or presenting symptoms occurred during or immediately after an unusual exertion, the disability was held compensable. In 1958, the Supreme Court of New Jersey, in the Ciuba case,[14] struck out the word *unusual* and called the *usual-unusual* test to be an illusory criterion of work-connected injury.

Katz[15] has stated that "Work, one's vocation, like play, one's avocation is a normal state of affairs . . . therefore, work to which one is accustomed cannot be considered detrimental per se. One would have to blame sleep and taxes (to pick out two other unavoidable events in our existence) as much as work for cardiac disability. I cannot understand why an employee who develops a heart attack at work should be considered to have developed it because of the work any more than one would blame sleep when such an attack occurs during sleep. Of course, if it can be shown that an employee was subjected to any excessive stress not ordinarily sustained on the job, the situation would be different."

In a similar vein, Sprague[16] concurs, explaining that "City living itself shortens life as compared to rural living, but most men are probably willing to sacrifice something for the comforts and amusements of the city. Industry should not be held automatically responsible for the hazards of life. Workmen's compensation was not intended to be a substitute for pensions and sickness insurance. The ordinary activities of living produce similar circumstances to those of employment during which, a chronic, slowly developing heart condition may be revealed. Less than one quarter of a person's life is spent on the job with a forty-hour week."

These differences of opinion between medical and legal authorities have raised new obstacles to the employment of cardiac subjects

and engendered decreases in productivity. Add to these differences the fact that some lawyers are dedicated to securing the largest financial settlement possible with the introduction into their cases of such factors as *aggravation, activation,* and *acceleration* and one can understand why the employer is loath to hire the patient with heart disease.[17]

With reference to *Old-Age, Survivors, and Disability Insurance,* payments under the disability feature of the program began July 1, 1957, and immediately the cardiologists noted an increase in cardiac disability in a certain few. Chest pain became more frequent and more crushing and breaths became shorter. And they applied for benefits. Of course, this legislation may be abused as evidenced by the following example of a 48-year-old patient who had suffered a myocardial infarction. He had already received Veterans Administration benefits for a service-connected hypertension. Following the myocardial infarction, he received 100 per cent disability from the Veterans Administration. He recently stated that he expects to retire in 2 years. Why? "Well you see," he stated, "By then I will be 50 years of age and when I combine the Veterans Administration money with the Social Security money, there will be no need to work." There is no question that occasionally such legislation breeds lack of incentive and thereby contributes to cardiac disability. It is hoped that such instances are few.

With reference to *Temporary Disability Insurance* and *Health and Accident Plans,* again, there may be abuses, especially, if the differential between the previous take-home pay and the insurance benefit is small. The onus of deciding the length of disability is always placed upon the shoulders of the private physician and there is often a tendency to extend the time of disability in order to please the patient. Unintentionally, the physician prolongs cardiac disability by making work unnecessary.

Resources for Rehabilitation

The Individual

In order to return the patient back to work and integrate him into the community structure, many resources are available. Probably first and foremost are the patient's own individual resources, depending upon his functional capacity, education, emotional background, and motivation. Next in importance is the physician, and, finally, various local and governmental agencies.

It has been said[18] "in order that people be happy in their work, these three things are needed. They must be fit for it. They must not do too much of it. And they must have a sense of success in it." We must accept the philosophy that work is the normal part of living and that work is important for the physical and emotional well being of the individual.

The Physician

Of all the resources, the enlightened physician provides the greatest impetus to rehabilitation. The strides that have been made in this field make it imperative that the physician fully understand the determination of cardiovascular fitness.[19, 20] In order to advise a patient whether or not he can go back to the same job, should change jobs, or even stop work altogether, he should know the stress of work involved and the energy cost demands on the job as well as at home. The work prescription should include evaluation of housework demands on the woman, recreational demands, travel demands, and the specific problem of work itself. The work physiologists have tabulated the great majority of human activities in form of energy demands and the physician should become familiar with them.[21] He would then realize that the majority of American workers are working at a level of 3 to 4 calories or less per minute, with most industrial jobs varying from 1.25 to 3.0 calories per minute and peak loads varying from 1.5 to 4.5 calories per minute. Realization by the physician that most patients can return to former jobs, or to the same job with relief of peak loads goes a long way toward facilitating rehabilitation of the cardiac patient.[20] Cooperation with the industrial physician in on-the-job evaluation is another important task.[22]

Ability to make knowledgeable use of health

an welfare services in the hospital and the co mmunity is increasingly important to the ph sician as new discovery results in greater sp ialization of function in the treatment pr ess. Facilities designed to assist the patie t to adjust to his life situation continue to evelop. This task may at times seem to be n exorbitant demand on the time of the ph sician who is already harried in keeping up with the exactions of his practice and the de ands of advancing medical knowledge, but in the long run, these resources will prove a valuable asset and may prevent time lost through poorly directed efforts.

In short, it behooves the physician to get acquainted with others concerned with helping the disabled. Interprofessional communication is vital to this process. The best of intention to cooperate may be thwarted unless there is a disposition on the part of all to understand each other and the respective roles and methods of each. The physician may take advantage of other disciplines in any stage of the cardiac disability, whether it be the acute stage, the convalescent stage, or the stage of rehabilitation.

The physician may enlist the help of the medical social worker. This professionally trained person may be of great assistance in helping the patient utilize medical care to the best possible advantage. The medical social worker will assist in the understanding of the emotional factors that promote or block treatment. By relating the social situation to the treatment procedures, the social worker provides the physician an added dimension in treatment.

Homemaker Service may be enlisted when the patient is a mother; explanation of and exploiting of temporary disability insurance may be made; and perhaps, referral to an agency for assistance if the family is in need of care, may be done. All these problems fall within the realm of the social worker. Certainly, the physician is in no position to do all this.

Again, in the stage of convalescence, the social workers may have a valuable role in many cases. They again may relate the illness to the family situation and provide community facilities when necessary. They may help in securing special medication. They may enlist the help of the Visiting Nurse Association or Homemaker Service. They may refer to the Housing Authority when it is found that the home is not adequate or appropriate in view of the patient's illness. They may work with community agencies by keeping them informed of the patient's condition at all times so that the help given is based on definite need in accordance with the illness. If the convalescence becomes more protracted, they may be able to refer the family to an agency for assistance if there is need.[23] There are many instances in which the employment of the trained social worker will tide the patient over the convalescent stage; make for smooth, continuous, unhurried and unworried convalescence; help the family ride out the storm until the wage earner is able to return to work.

If the physician feels inadequate to evaluate the patient's work capacity or if the patient is not rehired or cannot return to his former employment, there are other facilities at his disposal.

Voluntary Agencies

The Work Classification Unit of the Cardiac Clinic

There are over 40 Work Classification Units in the United States serving approximately 2,000 patients a year.[24] This may seem to be an infinitesimal service but their influence lies in the research and the interest they have created. The purposes are education, research, and service. The ideal team consists of a cardiologist, psychiatrist, social worker, vocational counsellor, physiologist, nurse, clerks, technicians, etc. Such an ideal is rarely achieved, or, if achieved, rarely maintained. Most of the units accept patients only on a referral from the local physicians, industries, and state and voluntary agencies. The reports they give are competent and useful to agencies interested in placing these patients. They lack the vagueness that usually characterizes the report of the general physician and even the cardiologist. The vagueness has been the bugbear of placement counsellors.

The main problem we have encountered with

a Work Classification Unit of our Cardiac Clinic has been the maintenance of dedicated personnel. This stems logically from the inability to place many of the patients because of the factors mentioned earlier. It seems that such specialized services must be subsidized with labor and industry contributing. Only then will they be interested in the benefits that a Work Classification Unit can offer to the physician and the patient.

The Sheltered Workshop

This is often helpful in the patient with marked psychogenic overlay and in one who has been disabled for over 2 years. It provides a spirit of cooperation, raises the patient's morale, imbues him with independence, and frequently provides a stimulus for training. For those who cannot be trained and must remain on a permanent basis in the sheltered workshop, the small amount of income gained at least restores a spirit of independence, so that the cardiac patient need not turn to his children or to the community for every wish. Jezer's groundwork in this field with the "disabled" cardiac plan at the Altro workshop has been enlightening and encouraging. He found that after work schedules were increased, 30 per cent of the patients were able to find work in industry after 10 months of such training.[25, 26]

The Rehabilitation Center

This is an ideal setup, but there are so few. In the center is a program in which a patient can be observed by a team under work conditions prescribed after discussion between those in charge of the training program and those in charge of the medical care. Then gradually the program can be accelerated until the patients reach tolerance. The job he can do is worked out in a setting with people of various disciplines who are skilled at such things.

The American Heart Association

Contact of local heart associations will often be fruitful in offering guidance in the community. The American Heart Association has been helpful in cardiac-in-industry programs, research in the evaluation of work potential, education, study of state compensation laws, establishment of work classification units, and heart-in-the-home programs.

To these voluntary agencies must be added JOB (Just One Break) and other organizations such as cardiac clubs, which are important in providing further impetus for cardiovascular rehabilitation.

State and Federal Resources

State Employment Service

Most states operate a service for the handicapped. Upon recommendation of a physician, trained personnel give guidance, counselling, and selective placement to these disabled individuals.

Department of Education

Many states have organized programs for persons with heart disease under the age of 18. They offer vocational training classes and guidance clinics for the purpose of directing the young cardiac patient toward a permanent occupation in which he can limit his activity as his cardiac capacity becomes increasingly impaired.

Workmen's Compensation Laws and Second Injury Funds

Workmen's Compensation Laws were the earliest of the social insurances in the United States. It has been estimated that 60 to 80 per cent of the working population of the United States are covered by these laws which are enacted in all the states and territories. They were passed to meet the problem of the worker who is disabled on the job, to help the exigencies of the situation due to wage loss, heavy medical costs, and rehabilitation. They were enacted to protect not only the worker but also the beneficiaries against economic hardship. Prior to the development of these laws, the worker's only recourse was to the courts, where he could sue for damages. The unnecessary delays in such cases with the slow grinding of the legal processes were unduly detrimental to the worker who rarely had significant savings on which to fall back.

By establishing this form of insurance, the states and the federal government have implied that the costs of work-incurred disease or injury are a part of the cost of production.

These programs are exclusively state ones, with no federal aid. In some states, coverage is elective as far as the employer is concerned. In others, coverage is compulsory. In some, the program is part elective and part compulsory. There are wide variations in conditions of coverage, adequacy of benefits, and methods of administration. It is not within the scope of this paper to discuss the variations but all the programs have in common the following benefits: medical care; payments for partial disability, for permanent total disability; death and burial benefits. Payments for temporary disability are based on a proportion of the average wage, with both top and bottom limits placed on weekly amounts. States also specify the maximum period over which benefits may be paid for temporary disability.

There are 3 methods of financing workmen's compensation depending upon the provisions of the individual state: there is self insurance; insurance with a private carrier or payment to a state fund. In general, the employee does not contribute to financing workmen's compensation. The cost is carried by the employer in line with the philosophy that this is one of the legitimate costs of doing business. This explains the employer's responsibility and his desire to keep the costs down.

That Workmen's Compensation has contributed to the security of the worker is unquestioned. Critics point out many ways, however, in which this program has failed to fulfill its once bright promise. In many states claims procedures are cumbersome and costly. Benefit schedules vary widely from state to state, but tend to be far from adequate in provision of compensation for loss of earning power. While all state programs provide for medical care in two thirds of the states, the task of rehabilitation is left to other governmental or to voluntary agencies.

With reference to the attitude of industry toward the rehiring of workers, it has been pointed out that the crux of the problem is financial. Fortunately, many states have attempted to counteract the difficulty of rehiring an injured worker by developing "second injury" funds. This legislation provides that the employer of a person who previously received an injury shall be liable only for a part of the cost of a second work-incurred injury or illness with the balance to be paid by the second injury fund. The employee is paid the entire amount of the appropriate benefit, however, from the combination of sources. This legislation is found in the workmen's compensation laws of 43 states and has widely broadened the opportunities of the handicapped.

Office of Vocational Rehabilitation

Temporary disability insurance in 4 states, and workmen's compensation in all states have helped the disabled cardiac workers to maintain themselves during the period of rehabilitation. The extension of the Old Age and Survivors Insurance helps the permanently and totally disabled over the age of 50, but these programs do not meet all the needs of the disabled cardiac person who is vocationally handicapped, yet physically able to work.

This task is assumed under vocational rehabilitation programs. While the first federal measure providing grants to states for this purpose was enacted in 1920, vocational rehabilitation has begun to come into its own as an important resource rather recently.

In 1954, the Eighty-Third Congress added some significant amendments to the Barden-LaFollette Act of 1943. These were hailed as introducing a new era in vocational rehabilitation of the handicapped.[27] In order to qualify for these services, there are 2 requirements: the disability must be of a handicapping nature; there is a definite possibility that the person could benefit from the service whereby he would be able to return to gainful employment.[28] According to governmental regulation, the services include "Any goods and services necessary to render handicapped individuals fit to engage in a remunerative occupation."[29] The services include medical care, guidance, training, physical restoration, placement, and others as required to restore the person to gainful employment. The re-

habilitation counsellor is an important cog in this program. Outside the medical aspects of treatment, he is the one who carries the load of guiding the disabled person, of helping him to select his training facilities, of assisting him to find a job, and of interpreting to the employer what the handicapped person is able to do.

This is a state-federal program, with the states carrying responsibility for providing basic services. The federal government, in addition to administering the grants to states, provides technical consultation, and through its various grants, stimulates the development of special projects and research.

It can be seen that this is an important resource for the selective placement of patients with heart disease. The services vary from state to state depending upon the enthusiasm and efficiency of the personnel. The Massachusetts Division of Vocational Rehabilitation gives proof to this statement. They were instrumental in alleviating the financial burdens and problems imposed by cardiac surgery and added to those of preexisting chronic illness. Many individuals and families were spared from applying for public assistance for medical care by these services. Through the cooperation of many agencies and individual physicians with the staff of the Division of Vocational Rehabilitation, 101 patients received 102 operations and approximately 75 per cent of this group were at work within 5 months following the operation. They have demonstrated that although employment of cardiac patients presents serious problems in rehabilitation, it is not an insurmountable obstacle.[30]

Veteran Services

At times, the patient may be able to turn to the Veterans Administration for help, particularly, if the cardiac condition is in some way connected with a Service-incurred disability. It must be pointed out, however, that non-Service connected benefits are also among the oldest of all provisions for veterans. Medical, hospital, and rehabilitation facilities are available for non-Service connected ailments, provided the veteran stipulates his inability to pay for such care.[31] This occasionally arises in private practice and is not uncommon in clinic patients.

There is no question of the high caliber of work and rehabilitation done at these institutions. The Veterans Administration claims that 95 per cent of the cardiac patients are working, 86 per cent with skill acquired in training. Of those who were not working, one half stated that they were unemployed for reasons not related to their heart or circulatory disabilities.[32] These figures underscore the value of medical rehabilitation, vocational training, and placement service.

Temporary Disability Insurance

Sickness incurred while off duty may temporarily incapacitate the worker. Since it is off duty, it is often not covered by Workmen's Compensation, nor is it covered by unemployment insurance, which applies only to people able to work. Under the Old Age, Survivors and Disability Insurance, only permanent and total disability is covered, and that only for persons over 50. Therefore, temporary disability insurance has been devised. This again is a great social gain for the worker and permits income during the illness, convalescence, and period of rehabilitation.

Workers in 4 states are covered under temporary disability insurance programs. These are Rhode Island, California, New Jersey, and New York. In general, coverage is similar to provisions of unemployment insurance and requires employee contributions. The employer may insure under a State Plan or private carrier.[37]

For the self employed, Health and Accident insurance has met this need to some extent.

Old-Age, Survivors and Disability Insurance

For the cardiac patient who has become totally disabled because of his condition, the 1956 and 1958 amendments to the Social Security Act have been a boon, another important step forward toward support and maintenance of individual dignity. These amendments included *severely disabled persons 50 years or over and their dependents* as beneficiaries. In order to be eligible for this pro-

gram, the disability should be one in which the patient is unable to engage in substantial gainful employment and one which is expected to result in death or to be of long continued and indefinite duration. In order for the worker to qualify, he must be fully insured and have 20 quarters of coverage out of the 40 calendar quarters before he became disabled. Disability insurance benefits will be paid for as much as 12 months before the month in which an application for the benefits is filed. The previous law contained no provision for retroactive disability insurance payments.[33]

It is important to point out that the claimant must accept therapy and training designed to restore him to gainful employment. If after a period of time the person becomes able to work again before he reaches the age of 65, disability benefits are discontinued.

The task of determining the degree and extent of disability was assigned to the state vocational rehabilitation agencies or to other designated state services. Certain phases of cardiovascular symptomatology are highly subjective and might be difficult to evaluate. Judgment must then be rendered not only on the cardiac condition but also on the individual's ability to perform gainful work. This requires much administrative and highly technical judgment. A staff of medical consultants is maintained in order to offer unbiased opinion. Anyone who has examined these applicants will find that there are many who are totally disabled and will appreciate the benefits of this legislation.

Public Assistance

In all communities, programs of financial aid to needy individuals are available. These may be administered by county or municipal welfare offices, or, in some states, by district offices of state agencies.

This is an important resource to the needy person ineligible for any of the social insurances, or with needs inadequately covered by the insurances. Financial aid is provided for the needy aged, children who are in need because of loss of support of a parent through death, incapacity, or absence from the home, the blind, and the permanently and totally disabled. The central condition in this program is financial need, although there are inevitably other factors of eligibility which must be met. Increasingly, public assistance is developing a strong emphasis on services designed to rehabilitate the individual client of the agency and to strengthen family life.

Other Public and Voluntary Programs

The foregoing by no means exhausts the list of social resources that may be available to the patient. Children's services, both public and voluntary, voluntary family agencies, organizations devoted to a higher standard of health care, and many others may be utilized by the resourceful physician. In larger communities welfare councils will be the chief source of information on available local services. In small communities, the physician will find his county public welfare office to be the best source of information.

Future Goals in Cardiovascular Rehabilitation

In spite of all that has been accomplished in cardiovascular rehabilitation, there are still many fertile fields to explore and develop. The education of the public, labor, management, and the physician still must go on. One may reemphasize the necessity of dispelling some of the old concepts held by the practicing physician. This is not always so easy as it might seem on the surface. Perhaps, education of the medical student will be more profitable. The young, the impressionable student is now being taught rehabilitation aspects of medical care combined with social work technics in some institutions. This will, in time, bear fruit.

There is a great need for the education of social workers who hold many of the key positions in rehabilitation. In general, the more than 60 accredited graduate schools of social work in the United States and Canada are not increasing the numbers of graduates sufficiently to supply the increased demand for their services.

Increased facilities for rehabilitation throughout the country—a definite need—will

only stem from dissemination of knowledge and training of personnel.

A final objective of any over-all program of rehabilitation should be the revision of legal aspects covering the entire subject, looking toward mutual understanding among physicians, attorneys, labor, and management. This is needed to avoid prolonged litigation, unjust disability payments and to limit the employer's liability for employee disability, which is one of the great obstacles to the employment of the person handicapped with heart disease.

It must be concluded that an all-out effort by all parties concerned will be forced upon us, whether we like it or not. Our economy can ill afford the loss of production or the expense of retiring from work a large proportion of our ten million or more patients with cardiovascular disease.[34] A rational and workable common meeting ground for the worker, his labor leadership, industrial management, and state and federal governing agencies must be found. It is our conviction that the physician cannot remain aloof from rehabilitation measures and should accept the responsibility for leadership in their sound and progressive development. This is his moral and professional obligation.

Summario in Interlingua

Le serietate del impactos socio-economic demorbo cardiac pote esser mitigate importantemente per le effortio del medico de mobilisar le ressources que existe e in plus per le effortios coordinate del medico, del agente de assistentia social, del infirmera, del consulente de rehabilitation, del therapeuta occupational, e del therapeuta physic. Le presente reporto discute e analysa le factores social que determina le alte incidentia de invaliditate, le ressources que es disponibile pro le objectivos de rehabilitation, e le fines concrete al quales le rehabilitation cardiovascular debe visar.

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During catheterization of the right side of the heart in 2 infants with congenital heart disease ventricular fibrillation developed. In both the arrhythmia was terminated successfully with electric countershock by the external defibrillator. In 1 normal rhythm followed external defibrillation, in the other a severe bradycardia resulted and normal sinus rhythm was restored only after stimulation by the external electric pacemaker. Attention is called to the importance of constant electrocardiographic monitoring during cardiac catheterization and to the necessity for the immediate availability of an external defibrillator and pacemaker in the catheterization laboratory.

SAGALL

SYMPOSIUM ON SURGERY IN ACQUIRED VALVULAR DISEASE

Guest Editor: JOHN W. KIRKLIN, M.D.

Introduction

By JOHN W. KIRKLIN

THIS symposium is concerned with the surgical treatment of acquired valvular heart disease. Approximately 15 years of experience in the management of this problem by operative methods have been attained by the surgical profession in America. In the beginning, the operations were done by closed technics. Subsequently, some were done by an open technic under hypothermia and circulatory arrest. More recently, the use of extracorporeal circulation and open cardiotomy has been extended to the surgical treatment of certain types of acquired valvular heart disease. In the future, still other surgical technics may be brought to bear in the management of these problems. In regard to some lesions it remains an unsettled question whether operations should be done by closed or open technics. Hence today there are purely technical problems of approach to the valve upon which there is not unanimity of opinion.

Although today the clinical experience with the insertion of artificial valves is very limited, the future will bring a period in which it will be necessary to evaluate the results of operations utilizing the patients' own valvular tissues in comparison with the results of operations with the insertion of artificial valves. At present it is hazardous to predict which will be the preferable approach in every situation. This emphasizes the need for all of us accurately to evaluate our methods and results.

Not only are we faced with the task of perfecting and evaluating our surgical technics, but we are faced also with the task of refining our indications for operation. These depend basically, of course, upon the risk of the operation and upon the long-term result that can be obtained. Again, therefore, the need for accurate reporting of our results and our mortalities becomes apparent.

Finally, during this long phase of the development of the new field of the surgical treatment of acquired valvular heart disease, we must not lose sight of the individual patients at present coming under our care. Each of these patients must be carefully evaluated, and for each patient the best decision possible at the moment with regard to operation must be made. Likewise, the best technic available at the moment must be applied when indication for operation is clearly present. We have, therefore, the dual task of careful, considerate management of the individual patient and collection of accurate experimental and clinical data to allow even better management of the patient of the future.

Surgical Treatment of Acquired Valvular Disease as Viewed by the Internist

By WILLIAM LIKOFF, M.D.

IT IS an obvious fact that acquired valvular deformities may impose a serious mechanical burden upon the heart. Over the years it has been logical to hope that definitive surgical technics would be developed to alter these defects so as to restore normal cardiac function.

However plausible the need, the evolution of surgery for acquired valvular disease was delayed by the fear that the heart could not tolerate unusual manipulation and continue its necessary function. When it was established that the heart was remarkably durable and competent in the face of arduous operative interference, cardiac surgery developed with dramatic rapidity.

Today, approximately a decade after the first successful modern operation for stenosis of the mitral valve, the current and potential role of surgery in the treatment of acquired valvular disease requires examination. The title of this presentation implies that the medical profession holds an ambivalent view on the matter—one by the internist, the other by the surgeon. Unfortunately this was, and in many areas continues to be, true.

Trained in the unique promise of the direct approach, the surgeon has been an enthusiast. Sensitive to the slowly deteriorating pattern of many diseases, the internist has been reluctant to accord the surgeon a primary role in the treatment of cardiac ailments. This dichotomy should not persist. Perceptive reflection on the work accomplished in the past decade permits an evaluation based on experience and fact, not prejudice. Unfortunately both protagonists and antagonists must admit that much of this information was exploited far beyond its natural importance. The first acknowledgment today must be that all of the truth is not known even at the present time.

The material upon which these comments are based has been obtained from an examination of the surgical technics now being employed, their effects on the anatomy, pathophysiology, and the subjective and objective manifestations of acquired valvular lesions, the surgical morbidity and mortality rates, and the devolutionary pattern of valvular lesions that are untreated by surgery.

Surgical Technics

Modern cardiac surgery may be divided into the closed-heart and the open-heart technics.

In the closed technics the surgeon applies corrective measures to and within an intact functioning organ. With use of this approach operations have been developed for the correction of stenosis of the mitral, the tricuspid, and the aortic valves alone and in combination, and for insufficiency of the mitral valve.

Closed-heart methods require surgery to be performed in an irritable, constantly moving organ, the portals to which are limited in number, size, and utility. Furthermore, when the surgeon does enter the heart, he is compelled to operate in a field of circulating blood guided by the sense of touch alone. As a final burden he must endure all of his limitations while the capability of the heart to continue to work under this type of duress remains unpredictable.

For these reasons it appears that closed-heart technics are destined not to survive. Actually they represent a stage in the development of surgical technics. Although they remain a monument to those who fashioned their principles and a useful tool for those who have mastered their application, only the inadequacies of the current pumps and oxygenators permit their continued use.

From the Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

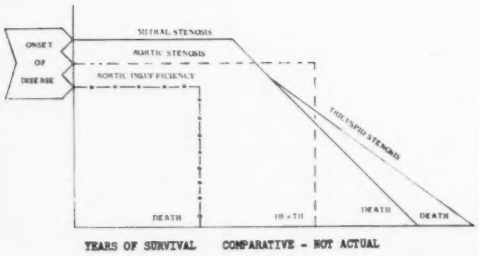

Figure 1

Comparative devolutionary patterns of acquired valvular heart disease. The horizontal line extends over the relative asymptomatic period.

It is freely predicted that simple efficient machines soon will completely free the cardiac surgeon from the limitation of not being able to see what he is attempting to correct or not being able to tailor his efforts precisely to the encountered need. For the present, however, open-heart technics have serious weaknesses. These mainly are related to the hematologic problems that arise from the need of priming the pump and from the intrinsic deficiencies of modern oxygenators. In addition, although the surgeon can view the lesion directly, he often is unable to evaluate function when the cardiac action is arrested.

In the present transition from immature to mature surgical methods technical inadequacies more than any other single factor account for the inability to depend upon surgery as the completely reliable answer to acquired valvular disease.

Results

In an understandable oversimplification of the problem the results of the surgical approach to acquired heart disease were at first measured in terms of symptomatic response. Indeed had a more vigorous demand been made of the early technics, it is questionable whether they would have survived to be developed into more effective methods.

Now the attainments must be evaluated more critically and along a broader base. The measures of anatomy, physiology, and function have been added to the analysis of the symptomatic response. All are interrelated. If the anatomic pattern of a valve is reconstructed without a return of its function, a useless result follows from which a significant regression of pathophysiology can hardly be expected.

The hallmarks of success in cardiac surgery are unmistakable. They consist of such findings as a disappearance of a pressure gradient, a decrease in cardiac size, and the quieting of a murmur. In short, results are definable in absolute terms. Therefore it must be emphasized that in the large area of paradox where symptoms are observed to improve but where no objective measurement of success is recorded, the correction and the lasting accomplishments are likely to be small.

Mortality and Morbidity Rates

Mortality and morbidity rates are sensitive indications of the maturity of surgical technics. The present operative mortality for mitral stenosis is recorded as 4 per cent and for mitral insufficiency by open-heart technics as 8 per cent.[1, 2] These compare favorably with the mortality rates now recorded for such abdominal procedures as cholecystectomy and gastrectomy. The mortality for the correction of aortic stenosis and aortic insufficiency by open-heart technics is now estimated at 20 and 25 per cent, respectively. It is to be recalled, however, that less than a decade ago the mortality rate for the correction of mitral stenosis stood in the same general area now noted for aortic stenosis. Furthermore, the mortality rate for gastrectomy a short 2 decades ago was in the same category.

It takes time to transmute failure to success, hesitancy to assurance, and death to life.

Devolutionary Patterns of Untreated Valvular Lesions

The internist is under a constant demand to outline the indications for the surgical treatment of acquired valvular disease. Fundamentally this problem is not a complicated one. The indications are determined when the available technics, the risks of their application, and their effectiveness are compared

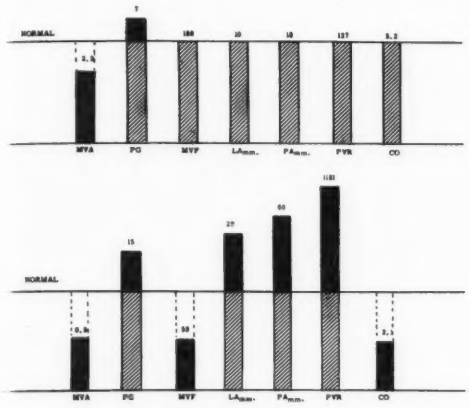

Figure 2

Top. *The earliest hemodynamic alterations in patient with mitral stenosis.* Bottom. *Abnormal hemodynamic data in patient with advanced mitral stenosis. MVA, mitral valve area; PG, pulmonary valve gradient; MVF, mitral valve flow; LA, left atrial pressure (mm. Hg); PA, pulmonary artery pressure (mm. Hg); PVR, pulmonary vascular resistance; CO, cardiac output.*

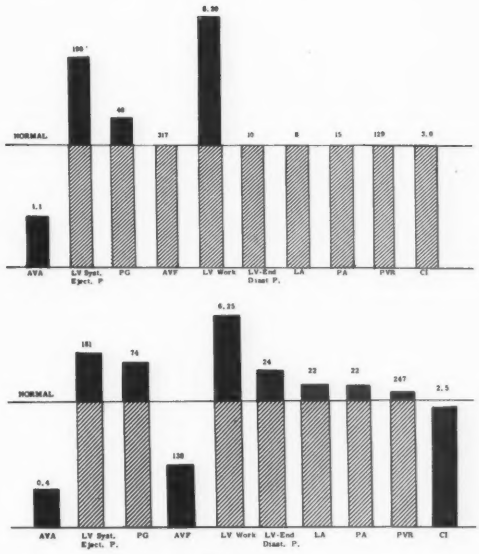

Figure 3

Top. *Hemodynamic changes in patient with early aortic stenosis.* Bottom. *Hemodynamic changes in patient with advanced aortic stenosis. AVA, aortic valve area, LV Syst. Eject. P, left ventricular systolic ejection pressure; PG, pulmonary valve gradient; AVF, aortic valve flow; LV Work, left ventricular work; LV-End Diast. P, Left ventricular end diastolic pressure; LA, left atrial pressure; PA, pulmonary artery pressure; PVR, pulmonary vascular resistance; CI, cardiac index.*

with the devolutionary pattern of the untreated lesion. The term devolutionary pattern has been adopted to indicate the general trend of events in the average patient who suffers from a specific type of acquired valvular disease. It has become increasingly apparent that each type of acquired valvular disease differs strikingly in the length of life it permits and the disability it causes.

Figure 1 illustrates the relative difference in the devolutionary patterns of 4 major acquired valvular lesions. It can be seen that mitral stenosis, relatively speaking, is a casual disease with a slow rate of deterioration. In dynamic aortic stenosis, however, the length of life is relatively short once significant symptoms develop.

Larger differences may also separate the pathophysiologic patterns within specific types of acquired valvular lesions. Figure 2 represents the earliest deterioration seen in mitral stenosis as compared with the most significant changes in advanced mitral stenosis. Figure 3 draws the same comparisons between patients with aortic stenosis. It is quite clear that the surgical treatment of acquired heart disease cannot be properly assayed for its immediate or chronic effect until it is clearly understood where in the devolutionary stage of the lesion treatment has been applied. Of equal importance it must be established at which phase of the devolutionary pattern surgical treatment is likely to be accompanied by the most effective result and the smallest mortality and morbidity risk.

Conclusions

Youth is brief. In its growth the surgical treatment of acquired valvular disease has offered the promise of an efficient mechanical answer to what in the final analysis is a mechanical problem. The promise of the future should not be confused with the accomplishments of the present. As technics improve,

the frequency and efficiency of their application must necessarily increase. For the time being results remain factually impressive.

Summario in Interlingua

Le periodo del juventute es breve. In su crescentia verso le maturitate, le tractamento chirurgic de acquirite morbo valvular ha offerite le promissa de un efficace responsa mechanic a un problema que, in le ultime analyse, es un problema mechanic. Le del futuro non deberea esser confundite con le attingimentos del presente. Si in le curso del tempore le technicas se meliora, il es evidente que similemente le frequentia e le successos de su application se augmenta e meliora. Le resultatos real que ha essite effectuate usque al tempore presente es certo impressionante.

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Transventricular Mitral Valvotomy

By FRANK GERBODE, M.D.

IN THE rediscovery period of mitral surgery, beginning with the efforts of Harken and associates[1] and Bailey,[2, 3] it was clearly demonstrated that even a moderate increase in the size of the mitral orifice would improve the physiologic status of the patient considerably. However, as time went on it was apparent that finger fracture alone was not sufficient for many badly scarred and calcified valves. This observation led to the use of various types of knife and other devices to increase the valve orifice and to obtain some degree of mobility. Historically, instrumental means to open the valve were thought an essential approach to the solution of valve stenosis.[4, 5] Thus, in 1912, Schepelmann[6] used the transventricular approach to cut the mitral valve in experimental animals. The first successful human operation for the relief of mitral stenosis was performed through the left ventricle by Cutler in 1923, an attempt having been made to incise the valve blindly with a tenotome.[7] A few years later Souttar[8] definitely demonstrated the feasibility and safety of finger fracture valvotomy. The belief that it was necessary to accept a degree of insufficiency in the effort to relieve the stenosis through instrumental means was questioned by Geoffrey Bourne in 1927,[9] who emphasized that, if possible, extending the commissures was preferable to an incision into a valve cusp.

In more recent history, Smithy, in 1948,[10] employed the transventricular approach with success in several patients, although regurgitation was still accepted by him as a necessary aftermath of the operation. DuBost and coworkers[11] introduced instrumental transatrial valvotomy, a blind operation that was done without simultaneous digital control. This definitely established the principle of opening the commissures by applying force in 2 opposite directions in an effort to obtain a good split of both anterior and posterior commissures.

Our own interest in the transventricular approach was stimulated by the work of Andrew Logan, of Edinburgh, and Oswald Tubbs, of London, both of whom have used transventricular valvotomy for some time. Our present approach is to make the conventional left lateral thoracotomy over the upper margin of the fifth rib, entering the fourth interspace. At times it has been necessary to cut the fifth rib anteriorly to gain access to the apex of the left ventricle. The pericardium is opened either anterior or posterior to the phrenic nerve, depending upon the amount of space available. A purse-string suture is placed around the base of the atrial appendage, but is not held with a tourniquet, for we have found that this not infrequently will result in cutting through the atrial wall, causing leakage; the operator usually holds the purse-string suture with his left hand. The valve is first palpated and efforts are made to open it digitally, for if a satisfactory valvotomy can be performed the transventricular approach is not used. However, if it is necessary to open the commissures more forcibly, we place a purse-string suture in the apex of the left ventricle in an area that is not supplied by large coronary arteries (fig. 1). A small rubber bolster is placed over the loop of the purse-string or mattress suture, so that in tightening it a cutting action will not result in the avulsion of ventricular wall. A small wound is made, and the instrument is passed into the chamber, where it is then guided through the orifice of the mitral valve with the right index finger in the left atrium.

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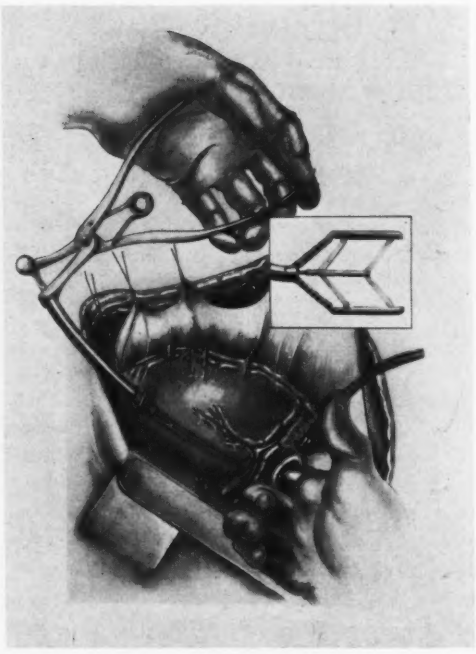

Figure 1

The instrument is passed through a small stab wound in the apex of the left ventricle. The small rubber bolster is used to prevent a cutting action from the apical suture. A screw in the handle can be regulated by the thumb to control the amount the blades may be opened.

The instrument* has a screw-lock in a convenient place on the handle, so that it can be opened gradually with the thumb as the blades are widened inside the heart. This is an added safety factor, for it will not allow the blades to spring apart maximally until the surgeon is ready for them to do so. The maximum spread is 5 cm. The instrument then is finally removed from the ventricle and the purse string is held by an assistant while a number of interrupted sutures are placed to close the stab wound, after which the purse string is removed. The purse string in the atrial appendage is simply tied as the index finger is withdrawn from the left atrium. The atrial appendage is oversewn with 000 silk.

*Manufactured by George P. Pilling & Son, Company, Philadelphia, Pa.

The use of this instrument in the majority of the operations since 1955 has not resulted in any severe instances of mitral regurgitation. There are occasional patients who will develop slight mitral regurgitation as a consequence of opening the valve widely, but this has not impaired their recovery, and there is no question in our minds that the more forceful splitting of the commissures has resulted in better mobility of the valve leaflets and a larger aperture.

In the past 200 operations upon the mitral valve with blind technics the operative mortality rate was 12.5 per cent. All the mortality rate can be accounted for by poor-risk patients, all of whom were in group III or IV. There have been no deaths in group-II patients, and very few group-I patients have been operated upon. In the last few years an increasing number of bad-risk patients have come to operation. Many of these had apical systolic murmurs and were formerly thought to have mitral insufficiency, but on more careful study have been shown to have had mainly tricuspid insufficiency associated with marked pulmonary hypertension. There have been 3 deaths from cerebral emboli, and it is an interesting fact that none of these emboli occurred during operation, but rather during the period following operation while the patients were in either the recovery room or ward.

Of special significance in patients with severe mitral stenosis is the anesthesia requirement. The services of an expert anesthesiologist are of primary importance. A technic for minimizing the amount of anesthetic agent has been developed by Bailey and associates[12] in which virtually no drug save Demerol is given during the major part of the operation, the patient meanwhile being maintained on 100 per cent oxygen until closure of the skin is started, when nitrous oxide is used. Such patients are semiconscious and can respond to commands during the cardiac portion of the operation.

Worthy of comment is our experience with operating upon 17 patients who had had a

previous mitral valvotomy in our hospital or by others. There were 2 postoperative deaths among the 17 patients, which is an indication that a second operation upon the mitral valve, done with the blind technic, is no more dangerous than the original one. One other patient has died from a vascular accident 3 years following a second operation. The average elapsed time between operations was 4 years and it is noteworthy that the majority of these procedures were done in the first 2 years following the introduction of mitral surgery. This is an indication that in many instances the operation was an inadequate one because of either severe fibrosis or calcification, or because the operator had not used more forceful means to obtain mobility and an adequate orifice.

The technic employed in second operations was to re-open the wound through the previous thoracotomy incision, which in most instances was a fourth-or-fifth-rib posterolateral or anterior thoracotomy. The incision was converted into a lateral thoracotomy. Only the portion of the lung that was adherent to the wound edges was separated sufficiently to permit the introduction of the rib spreader. Anteriorly the lung was separated from the pericardium, which was then gradually dissected free from the myocardium. In most instances this procedure required sharp dissection, but it was always possible to find a plane between the attached pericardium and the myocardium, and furthermore it was always possible to identify enough surface anatomy to avoid becoming involved with the major coronary circulation. One of the important steps in the dissection of the left atrium that has previously been entered for mitral surgery is the separation of the atrial wall from the inferior margin of the pulmonary artery. This separation must be carried well posteriorly, so that an adequate portion of the atrial wall can be made available for a purse-string suture (fig. 2). Usually the atrial appendage that has been tied is only a fibrous knot and, furthermore, the tissues surrounding it have become foreshortened from scarring. It may be necessary to carry the dissection well below the upper margin of the superior pulmonary vein. When this has been done we have employed a twisted stainless-steel wire as a purse-string suture, using a tourniquet to control it. The circle encompassed by the purse string need not be very great, for it is usually possible to make a stab wound in the center of it, directly entering the atrial chamber, and this can then be enlarged with a finger as it passes into the atrium. We have ordinarily placed the purse-string suture in the apex of the left ventricle before entering the atrium, for the transventricular approach has been used in virtually all of the second operations we have done. The same technic for opening the valve as employed with first operations is used (fig. 1). We have, however, been rather determined in opening the valve as adequately as possible, even at the risk of causing some valvular insufficiency in these patients. Suffice it to say that although we

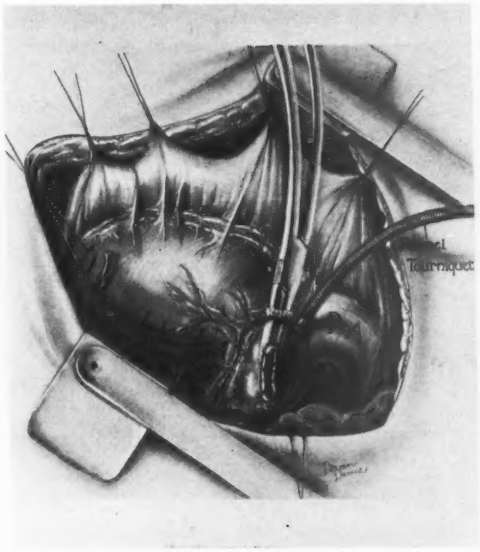

Figure 2

Exposure in second operations upon the mitral valve. A twisted wire is used for the purse string. It may be more advantageous to make a small stab wound through the atrial appendage scar, and follow it into the atrium with the index finger without using a clamp.

have created mitral insufficiency in some instances it has not been of such degree as to interfere with recovery. After the maximum fracture has been obtained, the index finger is withdrawn from the atrium as the wire purse-string suture is tightened. We then proceed with closure of the ventriculotomy incision and repair the atriotomy incision with a continuous suture of 000 silk. It is possible to remove the wire more easily by having a small suture looped in it as it is being placed, although probably no harm would come from leaving the wire.

It is currently being held by a number of surgeons that second operations on the mitral valve should be done with the aid of extracorporeal circulation. Although we have occasionally performed the open operation upon patients with predominant mitral stenosis complicated by other conditions, it is our impression that the open operation at the present time is not justified unless there is reason to believe that there are extensive thrombi in the atrium or associated mitral insufficiency of a significant degree. There are, of course, occasional patients who have combined tricuspid and mitral stenosis; these might reasonably be operated upon under extracorporeal circulation. Where the predominant lesion is mitral insufficiency we have, in favorable cases, operated with the aid of extracorporeal circulation. We are not convinced that direct vision is of very much aid in opening an extremely scarred and calcified valve. In fact, there are instances in which it is impossible to ascertain exactly where these commissures are, and it is likely that in the circumstances more insufficiency might be created.

The selection of patients for mitral valvotomy is almost entirely done on the basis of clinical findings with the aid of the roentgenogram and the electrocardiogram. Cardiac catheterization is only employed in dubious circumstances where other valvular disease or the degree of pulmonary hypertension seems worthy of evaluation. The operation is still performed ideally on patients in the younger age group, for although brilliant success can be attained from operations in those who ar in their fifties or occasionally in their earl sixties, the secondary effects of the stenosi will interfere with an outstanding result.

We have continued to use digitalis durin the preoperative period in patients, eve though it had not been used previously. Mo recently, in an attempt to convert those p tients who have fibrillated before operatio or who have fibrillated postoperatively, quin dine sulfate has been given, beginning a wee to 10 days following the operation. Many suc patients who have had an accurate valvotom can be converted and will retain sinus rhyth subsequently. If this attempt at conversio is not successful it is tried again severa months later.

Summary

In a consecutive series of 200 operations for relief of mitral stenosis, transventricular valvotomy was performed whenever digital valvotomy was found to be ineffective. The operative mortality was 12.5 per cent.

In a series of 17 second operations for mitral stenosis, the transventricular method was similarly used, with 2 operative deaths. A left lateral thoracotomy was employed, with reentry through the left atrium.

The results of transventricular valvotomy were more satisfactory than when the usual commissurotomy through the left atrium was employed.

Summario in Interlingua

In un serie consecutive de 200 operationes pro le alleviamento de stenosis mitral, le technica del valvotomia transventricular esseva usate quandocunque valvotomia digital se monstrava inefficace. Le mortalitate operatori in le serie total esseva 12,5 pro cento.

In un serie de 17 secunde operationes pro stenosis mitral, le technica transventricular esseva usate secundo le mesme principio. In iste serie il occurreva 2 mortes operatori. Thoracotomia sinistro-lateral esseva empleate, con re-entrata via le atrio sinistre.

Le resultatos esseva plus satisfacente in le casos in que valvotomia transventricular esseva usate que in le casos tractate per le methodo usual de commissurotomia via le atrio sinistre.

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Correction of Mitral Insufficiency under Direct Vision

By EARLE B. KAY, M.D., CID NOGUEIRA, M.D., AND H. A. ZIMMERMAN, M.D.

MANY ingenious closed or blind technics have been devised and enthusiastically advocated in the recent past for the surgical correction of mitral regurgitation. Invariably, success was transitory and such operations were short lived, to be replaced similarly by others. During the past 3 years we have operated upon 82 patients with varying degrees of mitral insufficiency by the open-heart technic. During this period there have been modifications and improvements in the technics, although the principles involved have remained essentially unchanged. For the first time, postoperative results have continued to warrant our initial enthusiasm.

Pathology

In 25 patients pure mitral regurgitation was found (table 1). There was generalized dilatation of the annulus fibrosus. The regurgitant jet was most pronounced through the posteromedial half of the valve orifice but also occurred in varying degrees throughout the valve. In only 1 patient was there a flail anterior leaflet from rupture of the chordae tendineae. More than adequate valvular tissue was present in all instances, even though in the majority there was some thickening of the leaflets with rolling of their edges.

Seventeen patients had predominant mitral regurgitation but with significant degrees of mitral stenosis. The valve rings for the most part were fairly normal in size. The leaflets and chordopapillary structures showed greater degrees of thickening, although adequate valvular tissue remained. The residual orifice was either centrally located and patulous or eccentrically located and of the tear-drop variety.

Twenty-one patients had predominant mitral stenosis but also had varying degrees of mitral regurgitation. The annulus in these patients appeared for the most part smaller in size. There was further thickening and absorption of the leaflets and chordopapillary structures. The majority also had varying degrees of subvalvular stenosis. For the most part these were rigid, incompetent valves. Four additional patients might be referred to as having destroyed valves from the viewpoint of significant valvular function. A rigid tunnel remained as a result of the fusion of contracted leaflets to scarred and fused papillary muscles.

In 8 patients the valve was destroyed by extensive calcification that extended in 3 instances into the papillary muscles and ventricular endocardium. Two patients had traumatic regurgitation resulting from previous attempts to relieve their mitral stenosis by means of the commissurotomy knife, and 1 patient had a hole in the anterior leaflet resulting from a previous subacute bacterial endocarditis. Four additional patients had incompetent mitral valves as part of congenital atrioventricularis communis. Knowledge of the etiology of the regurgitation is important, for it determines the type of surgical correction to be employed.

Advisability of Cardiac Arrest

The first 7 patients had their mitral valvular correction during elective cardiac arrest in the belief that there would be less risk of air embolism. It soon became apparent that the surgeon must have a knowledge not only of the structural changes but also of the relation between structural changes and functional changes. Functional changes in the case of valvular disease mean motion—the proper opening and closing of the valve. Nothing short of observing the valve mechanism in the beating heart gives the surgeon information of the pathologic physiology of that patient's valvular mechanism. The factors contributing to the regurgitation, the site of the regurgi-

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tion, and the effectiveness of the correction can all be assessed better with the heart beating.

The greater improvement in the results has borne out these observations, so that routinely all patients with mitral regurgitation are now operated upon with the heart beating. There are also additional advantages in maintaining cardiac action in that the myocardium is kept well oxygenated; the operation need not be hurried; the need to restart the heart is obviated; and there have been no associated arrhythmias in our series.

In the presence of combined lesions, particularly aortic regurgitation, the aortic valve is corrected first. Usually this has been done with direct coronary artery cannulation and perfusion, so that the beating heart is maintained. With the coronary cannulae still in place, and with the heart beating, correction of the mitral valve is then performed. In instances of subclinical aortic valvular involvement considerable regurgitation through the aortic valve and into the operative field may take place, particularly if there is undue traction against the aorta by the mitral retractors. As long as regurgitation is insufficient to influence arterial perfusion pressure, this excess blood is aspirated back to the oxygenator by means of the sump. In extreme cases, intermittent aortic occlusion for 2-minute periods is employed.

Recent advances in localized cardiac hypothermia in the range of 7 to 10 C. appear attractive and have been used in several instances in the presence of combined lesions. In the future this technic may be further employed during the insertion of complete mitral valvular prosthesis, when it is important to have a dry field and a quiet heart while the artificial chordae tendineae are sewed to the papillary muscles.

Selection of Patients

In the recent past, prior to an effective technic for the surgical correction of mitral regurgitation, considerable effort was exerted in the selection of patients for valvular surgery, directed at excluding patients with mitral regurgitation or multivalvular disease. Many diagnostic tests were employed to aid in this differentiation, including left-sided cardiac catheterization, Evans blue dye-dilution curves, and Diodrast studies. Now that we can successfully correct patients with mitral regurgitation it makes little difference whether this differentiation is made preoperatively. Furthermore, although these examinations in skilled hands are not associated with many complications, they are still formidable and frequently exhausting to the sick cardiac patient, in addition to which they frequently do not provide sufficient additional information. The need for the more precise preoperative information is less important, since it can be readily obtained at the time of surgical exploration by pressure studies and direct examination.

Table 1

Mitral Regurgitation (Pathology Found in Eighty-two Patients)

Type	No. of cases
Pure regurgitation	25
Predominant regurgitation, significant stenosis	17
Predominant stenosis, varying degrees of regurgitation	21
Destroyed fibrotic regurgitant, stenotic valve	4
Destroyed calcified regurgitant, stenotic valve	8
Traumatic regurgitation	2
Hole in anterior leaflet (previous subacute bacterial endocarditis)	1
Incompetent mitral valves (part of atrioventricularis communis complex)	4
	82

Preoperative Evaluation

The history, clinical course, and physical examination still remain very important aspects of the appraisal. The electrocardiogram and roentgen examinations give valuable information of chamber hypertrophy and dilatation. It is particularly valuable to have earlier studies available for comparison to determine whether significant change or progression of the disease has occurred. Phonocardiograms are employed for comparison with postoperative studies. A definite im-

provement in valve sounds is now being observed, which was very infrequent in patients operated upon with the closed technics. Right-sided cardiac catheterization, with and without exercise, a simple and entirely safe procedure, is routinely employed to determine the status of and changes in the pulmonary vasculature, as well as to give information regarding cardiac output and reserve. Pulmonary wedge pressure studies obtained at this time not only provide an index of left atrial pressures but also provide suggestive evidence as to the presence of regurgitation or stenosis, or both. We have found the pulmonary wedge pressures to correlate closely with left atrial pressures obtained at operation. Furthermore, such preoperative objective findings are invaluable for postoperative evaluation. We are now attempting to obtain such data preoperatively, at the operating table, prior to discharge, 6 months postoperatively, and again several years postoperatively, to obtain as complete an understanding as possible of the hemodynamic changes.

It is important to determine the presence or absence of rheumatic activity by sedimentation rates, the presence of C-reactive proteins, and a period of observation in the hospital of temperature and pulse. Liver and kidney function tests are employed when indicated. In some instances a longer period of observation is necessary to determine the patient's response to definitive therapy in the presence of failure.

Criteria for Recommending Surgery

If the studies show the patient to be symptomatic, to have an enlarged heart, electrocardiographic evidence of left atrial and ventricular overloading, evidence of pulmonary hypertension aggravated by exercise and without signs of activity, operation is recommended. This is particularly so if serial examinations reveal a definite progression in such signs, especially with regard to the x-rays and electrocardiograms. An increase in the size of the cardiac silhouette as well as a progressive shift of the mean electrical axis to the right, an expression of aggravated pulmonary hypertension, constitutes important evidence. The cardiopulmonary reserve is frequently relatively good in patients with mitral regurgitation. Once these signs appear or there is evidence of progress, we believe it is unwise to postpone operation because of the detrimental effect on the myocardium, which may compromise an otherwise successful result.

Present Outlook of Surgical Correction

Approximately 85 per cent of the patients with mitral regurgitation can today be greatly benefited by surgical correction by the open technic and can be restored to a useful healthful life. In the remaining group of patients not helped or in whom there is a high surgical risk, 3 facets of the problem remain to be corrected or improved. These problems pertain to the heart, the type of pathology, and the surgical correction.

To be reasonably successful the surgeon must have a patient with sufficient myocardial reserve to withstand the operative procedure, a valvular mechanism that is not so severely destroyed that it cannot be surgically corrected, or a surgical technic by which to make this correction in the presence of a destroyed valve. In contrast, the surgeon is unlikely to be successful in a patient with severe myocardial failure, a badly destroyed valve, and without a technic for complete valvular replacement for those valves that cannot be benefited materially otherwise. It is not meant to imply that all 3 of these aspects of the problem go hand in hand, for a patient with a relatively good valve from a technical point of view may have a severely dilated and hypertrophied heart. These problems, however, are responsible for the morbidity and mortality and require further emphasis and improvement.

The first facet of the problem is the myocardial reserve of the patient. The incidence of "last resort" surgery is unquestionably too high. Until recently there was no effective means for surgical correction. Insufficient myocardial reserve to tolerate the operative procedure is one of the main causes of failure. The surgeon may improve the valve markedly,

ith lowering of the left atrial pressure, only see the heart fail because of its inability to ithstand the operative procedure or to pump gainst the severe pulmonary vascular resistnce. Now that there is an effective technic, is phase will undoubtedly improve with ne. Patients will be seen earlier by the surgeon while they are in relatively good general ondition. When it is evident that the disease significant or progressive, operative intervention should be recommended before obvious myocardial failure or extensive pulmonary vascular sclerosis develops (fig. 1).

The second facet of the problem is the pathologic state of the mitral valve. A small percentage, perhaps 10 per cent of the valves, are so severely destroyed that with past technics they could not be salvaged. A destroyed valve that cannot be sufficiently corrected to improve the hemodynamics has been the most common cause of failure in the past (fig. 2). Success in this group means the solution of the final problem—that of the surgical correction by complete valvular replacement with an artificial valve. Such a valve has been developed in the laboratory made out of woven Teflon fabric and patterned after the normal anatomic valve with leaflets and chordae tendineae (fig. 3).* This valve holds much promise for future correction of severely destroyed valves.

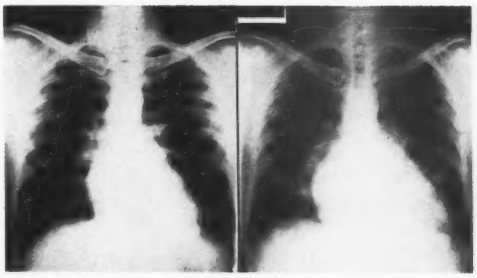

Figure 1A

Roentgenograms of patient with mitral regurgitation demonstrating progressive cardiomegaly over a 2-year period prior to surgical correction. Cardiopulmonary reserve still satisfactory.

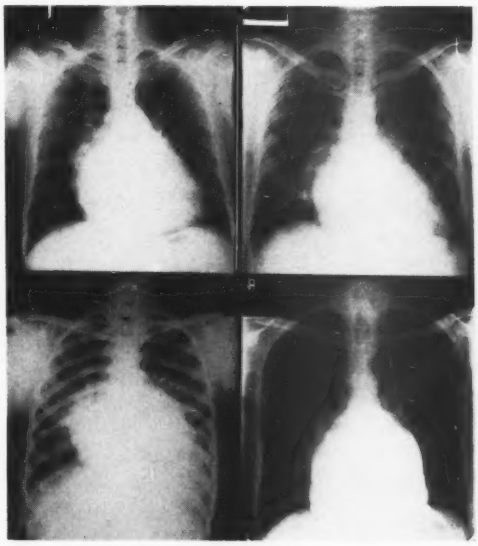

Figure 1B

Roentgenograms of patients with mitral regurgitation demonstrating severe cardiomegaly and pulmonary congestion. Surgical correction recommended prior to the development of this stage.

Surgical Technics

Pump-Oxygenator

All of the patients have been operated upon with the use of the Kay-Cross rotating disk oxygenator. A flow rate usually of 50 ml. per Kg. per minute, which results in an arterial inflow of 3 to 3.5 liters per minute, has sufficed to maintain a mean arterial pressure of 70 to 80 mm. Hg. The inflow cannula is always in the common femoral artery through the superficial femoral artery. There is controlled venous return regulating the vena caval flow by maintaining the vena caval pressure at prefusion levels. This, we think, gives better control over body blood balance. Constant monitoring of the mean arterial pressure, mean vena caval pressure, electrocardiogram, electroencephalogram, pO_2, pCO_2, and pH, body and oxygen temperature, provide a constant physiologic status of the patient. Hematocrit, hemoglobin, and body weight are determined immediately prior to and following surgery.

As an anterolateral incision with transection of the sternum is made, the femoral can-

*Valve developed in conjunction with the United States Catheter Corporation, Glen Falls, N. Y.

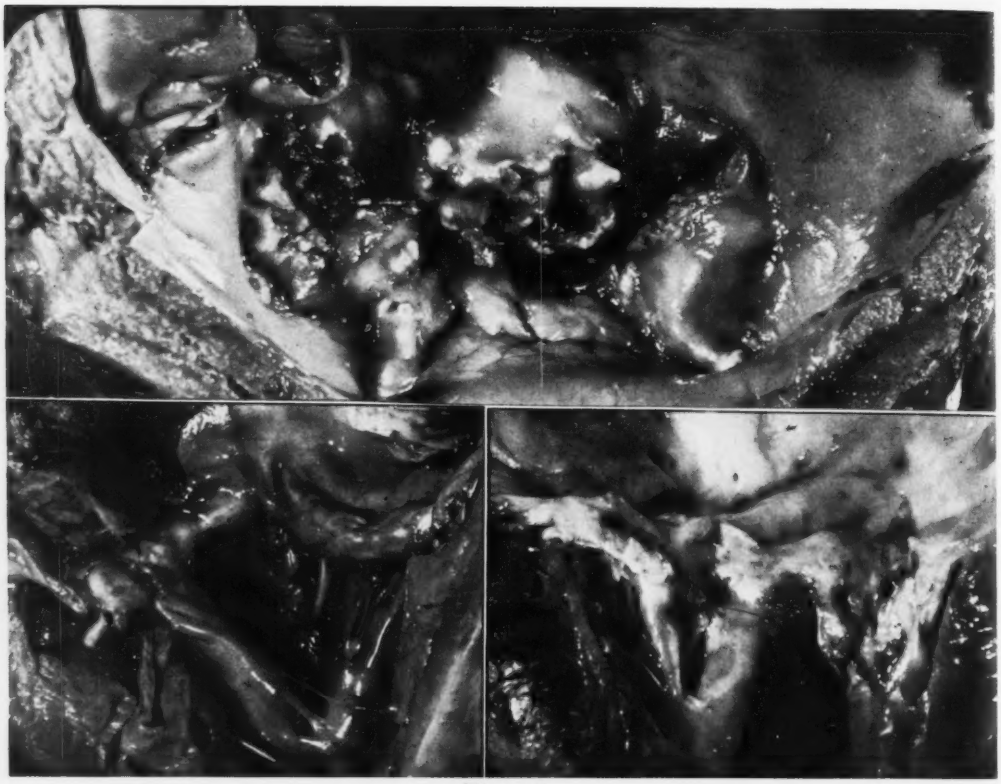

Figure 2

Severely destroyed fibrous and fibrocalcific mitral valves. Improvement possible only by complete excision and replacement with artificial valves.

nulations for arterial input, arterial manometer, and intravenous infusion are simultaneously completed.

Exploration and Visualization of the Valve

A routine re-evaluation of the heart is first made. The status of the tricuspid valve is determined by digital exploration. Pressure recordings of the aorta and left ventricle are then obtained to verify or eliminate coexistent aortic valvular disease. Pressure recordings of the pulmonary artery and left atrium are then made. The extracorporeal perfusion is then begun while the left atrium is incised and the mitral valve is digitally explored. If the mitral valve is obviously incompetent, the sump is introduced into the left ventricle through the mitral valve to make sure ventricular systole is ineffective in pumping blood or foam through the aortic valve. The various factors contributing to the regurgitation are visualized and assessed. If a significant degree of stenosis is also present, the valve is opened as widely as possible digitally, and then the sump is inserted between the valve leaflets into the left ventricle. The commissurotomy is then completed under direct vision, with mobilization of the valve cusps, chordae tendineae, and papillary muscles. Then the insufficiency is corrected.

Repair of Valve

Pure Regurgitation

The principle of annular plication, to reduce the size of the dilated annulus and in turn to approximate the valve leaflets, is still employed

nitially, the annular plication was made pri-
arily at the level of the anterior and pos-
erior commissures (fig. 4), by approximating
he annulus above and below this site with
everal mattress sutures. In at least 2 patients
hese sutures tore out of the heart wall and
nnulus during the postoperative period. Con-
equently, the next modification was to insert
he sutures through sections of compressed
valon so that the tension was against the
valon rather than the cardiac wall. Here
gain, however, in 1 patient with a huge heart
nd severely dilated annulus, the sutures
ulled out from the heart. Initial improve-
ment was excellent in that the left atrial pres-
sures fell from 60/24 to 14/11 mm. Hg. It
was apparent that in greatly hypertrophied
hearts several sutures even when reinforced
with plastic material were insufficient to main-
tain the reduction in the size of the annulus
in all instances. Therefore, the principle of
multiple fixation was then employed. In this
technic, sections of an annular piece of Teflon
felt, of varying length but smaller than the
dilated mitral annulus, are fashioned. The
middle of this segment is sutured first at the
level of the posterior commissure. The anterior
and posterior ends of the felt are then sutured
as far laterally on the anterior and posterior
aspects of the mitral annulus as appears neces-
sary to correct the insufficiency. The anterior
and posterior limbs of this circular felt are
considerably shorter than the corresponding
segments of the mitral annulus. Then a run-
ning suture, taking larger bites of the annulus
than of the Teflon, fixes the dilated ring to
the plastic, thereby reducing the size of the
dilated annulus in a circular fashion by mul-
iple points of fixation. If necessary, a second
partial circular segment of Teflon is employed
in a similar manner, beginning at the level of
the anterolateral commissure. It is important
to overcompensate slightly for the dilated an-
nulus, for its size is smaller in the heart
empty of blood than when it is again dis-
tended with blood. In the instance of the flail
leaflet resulting from ruptured chordae ten-
dineae, this leaflet is sewn to the remaining

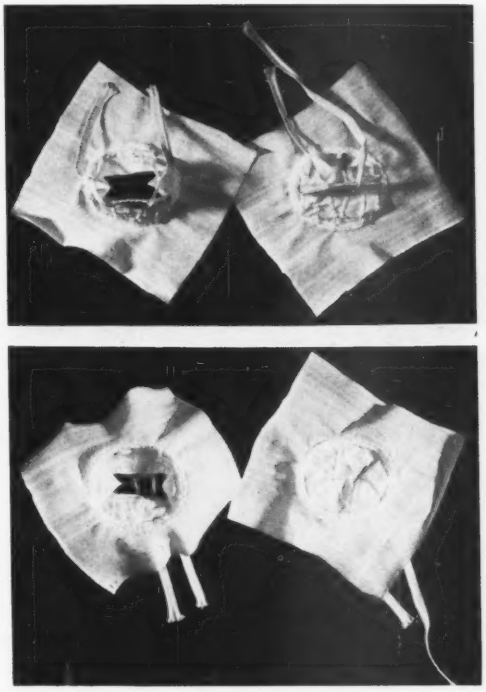

Figure 3

Mitral valve prosthesis patterned after the normal mitral valve with leaflets and chordae tendineae. The valve is made from woven Teflon fabric. Upper, *ventricular aspect;* lower, *atrial aspect.*

chordae tendineae and papillary muscle. If necessary, artificial chordae tendineae could be employed.

Combined Lesions

In patients with mixed stenosis and regurgitation it is important that a complete commissurotomy and mobilization of valve leaflets be accomplished prior to correction of the insufficiency. Our interpretation today of a complete commissurotomy differs from previous teachings in that the fused commissure is a pathologic and not an anatomic entity, and as such the separation of the 2 fused leaflets should not be taken to the mitral annulus as previously recommended since regurgitation would then occur at these sites. In reality the mitral valve is a sleeve valve divided into a large anterior leaflet, a smaller posterior leaflet, and small lateral and medial

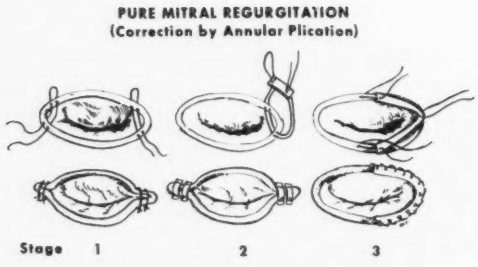

Figure 4

Stages in development of present technic of surgical correction by annular plication with multiple point fixation.

leaflets. In some instances these small lateral and medial leaflets may not have developed completely as such but do exist as functional valvular tissue joining the anterior and posterior leaflets and preventing regurgitation at these sites.

Frequently, the rolled inverted leaflets fused with the chordopapillary structures can be separated by sharp and blunt dissection, providing both greater mobility and functional valve surface. Over fifty per cent of the patients have had significant subvalvular stenosis with complete fusion of the leaflets to the papillary muscles with absorption of the chordae tendineae. In such instances it is impossible to perform the commissurotomy or valvuloplasty in the usual manner. We have found that in this type, the dissection is best begun peripheral to the fused commissure (fig. 5). An instrument is inserted at this site through the fused leaflets to delineate the exact relationship of the fused papillary muscles to the leaflets. Care has to be exercised that each leaflet be left with sufficient papillary support. The incision in these fused leaflets is then carried centrally so as to be centered over the fused papillary muscles, which are then incised into 2 equal segments down to the ventricular endocardium. A variety of technics has been employed in the correction of the residual insufficiency, including the addition of valvular tissue in the form of partial plastic leaflets or selective annular plication. Care must be exercised not to reduce significantly the size of the frequently restricted mitral annulus. In some severe types with complete loss of valvular function with absorption and scarring of the valvular components, only partial correction can be obtained at best. Such patients do not comprise over 10 per cent of the entire group. Such lesions in the future will undoubtedly be corrected by complete valvular prosthesis.

The 2 patients with traumatic regurgitation, secondary to the laceration of the leaflets by the commissurotomy knife during surgery for mitral stenosis, were treated by completing the valve mobilization as described above, then by resuturing the lacerated leaflets, and by reinforcing the sutures with pledgets of plastic material.

Calcified Valves

Approximately 30 per cent of the patients with combined lesions have varying degrees of calcium deposits in their valves. For the most part this is of little concern and in no way compromises an otherwise successful correction. In 8 patients in this series (10 per cent), the degree of fibrocalcific destruction not only caused complete loss of valvular function but also prevented any significant correction by past technics. In the first 5 it was obvious that little had been accomplished. All of these patients died during the postoperative period from lack of significant hemodynamic improvement. It was apparent that success in this group required excision of the diseased valve and replacement by a complete valvular prosthesis. During the ensuing months all patients were carefully screened with the image amplifier, and those with extensive calcification were excluded from surgery. During this period of time a complete artificial valve was developed. Preliminary laboratory observations of the valve indicated that it would be suitable for valvular replacement. This valve has now been used in 3 instances. Unfortunately there are no survivals as yet. However, the valve appeared to function well in each patient with considerable drop in left atrial pressure. Two of the patients died from renal complications; the longest survival was

days. This patient died immediately following overperfusion with the artificial kidney, employed because of a renal shutdown. He had had known multiple infarctions of the lungs and kidneys preoperatively. The third patient had been operated upon 5 years previously for mitral regurgitation by the closed technic. She had had severe ventricular failure preoperatively, and little myocardial reserve. Autopsy examination in all 3 patients revealed no complications related to the artificial valve.

Results of Surgery

Since this paper pertains primarily to rheumatic mitral regurgitation, the results of surgery and the postoperative evaluation will be based on those patients whose significant defect was the mitral valvular lesion due to rheumatic fever (table 2). Those patients with multivalvular surgical correction are eliminated from the group in this discussion, as well as those of the congenital variety.

Pure Mitral Regurgitation

In 18 of the 25 patients with pure mitral regurgitation the disease was limited primarily to the mitral valve. There were 2 deaths in this group; an operative mortality of 11.1 per cent. One of the deaths resulted from air embolism; this complication has now been eliminated in the last 62 patients. The second death occurred 3 months postoperatively in an 11-year-old boy with severe pulmonary hypertension, marked cardiomegaly, poor myocardial reserve, and greatly reduced pulmonary reserve from pulmonary vascular sclerosis and atelectasis.

Death from air embolism in the future should be preventable, since the conditions conducive to its occurrence have been determined and eliminated. In regard to the second death, we realized preoperatively the desperate risk involved but accepted it, knowing in advance that it was the boy's only opportunity. In the future it is hoped that few cases of this severity will be seen.

Of the 16 surviving cases in this group, 13 have been operated upon 3 months to 2 years

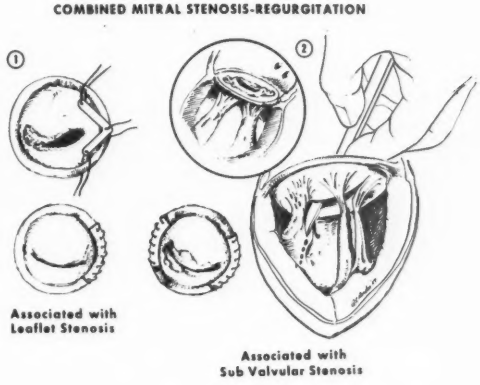

Figure 5

Sketch of technic employed in the surgical correction of combined mitral stenosis and regurgitation.

previously, not long enough to know their eventual course but long enough to provide some indication of possible benefit. In 2 patients done early in the series, initial improvement was followed in 3 to 4 months by recurrence of evidence of their mitral insufficiency. Both had huge hearts, and in both the surgical correction by annular plication was performed in the original manner without the re-enforcing plastic sutures or the more recent technic of multiple point fixation. The murmur has returned in both, and it is thought that the sutures have torn out. A third patient, a 56-year-old man, has had very significant clinical improvement, with resumption of activity and loss of the systolic blowing murmur, but his physicians reported no reduction in the pulmonary artery pressures at 6 months. The other patients have all been greatly improved. In the other 2 patients with catheterization studies, the hemodynamic data have returned to normal. In one the pulmonary artery pressures fell from 37/18 to 25/11 mm. Hg and in the other from 47/16 to 28/14 mm. Hg.

Mixed Lesions—Predominant Regurgitation

There has been 1 death in this group of 17 patients who had predominant mitral regurgitation with varying degrees of mitral steno-

Table 2

Mitral Regurgitation

Type	No. of patients	Operative mortality	Significant improvement (3 months to 2 years) clinical hemodynamics	
Pure	18	(2) 11.1%	84.6%	2 of 3
Mixed				
Predominant regurgitation	17	(1) 5.8%	85.7%	5 of 6
Combined (pliable valve)	21	0	95%	6 of 6
Destroyed				
Fibrotic	4	(4) 100%		
Calcified	8	(8) 100%		
Traumatic				
(Previous commissurotomy)	2	0	100%	1 of 1
Hole in anterior leaflet				
(Subacute bacterial endocarditis)	1	0	100%	

sis. From the technical viewpoint, the satisfactory correction of the stenosis and of the insufficiency could be relatively easily obtained.

Of the 16 surviving patients, 14 have been operated upon between 3 months and 2 years. Twelve (85.7 per cent) have had marked clinical improvement, 1 moderate improvement, and 1 no improvement. Six of these patients have had catheterization studies from 3 months to 1 year postoperatively. In 5 patients there was significant hemodynamic improvement.

Combined Lesions

There were 21 patients in this group with predominant mitral stenosis and varying degrees of regurgitation. They did not show the same degree of cardiomegaly as the 2 previous groups, nor such severe pulmonary vascular findings. There were no operative or late deaths.

Twenty patients have been operated upon 3 months to 2 years previously. All these patients but 1 have shown marked clinical improvement. In this patient the stenotic lateral commissure was severed at the annulus fibrosus, so that the valve was incompetent. This defect was subsequently corrected surgically with what appears initially to be a successful result. Six have had catheterization studies from 9 months to 2 years after operation; 5 have essentially normal hemodynamic findings, and the sixth showed significant improvement.

Destroyed Valves

There were 4 patients with rigid stenotic incompetent valvular tunnels for which no significant operative correction could be obtained. In addition, 8 patients had severely calcified valves, in 5 of whom no significant operative improvement could be obtained by previous technics. All these patients, unimproved by surgery, died during the postoperative period. Three patients with destroyed calcified valves had valvular replacement by complete artificial valves. There was marked hemodynamic improvement in these 3 but they all died, 2 from renal complications and the third from myocardial failure.

Summary

The incompetent valves in the majority of patients with mitral regurgitation can be surgically corrected by the technics described above. The ease and effectiveness of the correction are largely dependent upon the severity of the pathologic process. The roles of chronic myocarditis, myocardial failure, pulmonary vascular sclerosis, and the presence of other valvular defects are important factors in the eventual result. Fortunately, the abnormality in the majority of valves can be corrected, and the myocardial reserve is us-

always sufficient to provide satisfactory function. With continued progress in this field, earlier surgical intervention, and probably less severe disease from improved treatment, better results can be anticipated in the future.

Summario in Interlingua

In le majoritate del patientes con regurgitation mitral, le incompetente valvulas pote esser corrigite per le technicas describite in le presente articulo. Le facilitate con que le correction pote esser effectuate e le efficacia del resultatos depende in grande mesura del grado de severitate del processo pathologic. Le presentia de myocarditis chronic, de disfallimento myocardial, de sclerosis pulmono-vascular, e de altere defectos valvular es importante factores in le determination del resultatos a longe vista. Felicemente, in le majoritate del valvulas il es possibile corriger le anormalitate, e le reserva myocardial es usualmente adequate pro provider un functionamento satisfactori. Quanto al futuro, il es justificate expectar melior resultatos, non solmente in consequentia de continue progressos in iste campo e de plus precoce interventiones chirurgic sed etiam proque le severitate del morbo va esser reducite per plus efficace modos de tractamento.

Open Operation in the Treatment of Calcific Aortic Stenosis

By JOHN W. KIRKLIN, M.D., AND HAROLD T. MANKIN, M.D.

AFTER experience with the surgical treatment of calcareous aortic stenosis by closed technics and by an open technic with hypothermia, we have adopted an open technic utilizing extracorporeal circulation. Extracorporeal circulation was first employed for the relief of acquired stenosis by Lillehei and associates,[1] although their published report indicates that their attempt was primarily to open the fused commissures. Bailey[2] emphasized the singularly important advantage of removing the calcareous deposits from the leaflets in order to obtain greater valvular flexibility, and his experience proved that this is technically feasible.

Material

Our experience with the direct approach to the stenotic aortic valve began in January 1959. This report is based on the 14 consecutive cases with operation between then and October 1.*

Preoperative Status of Patients

The pertinent clinical data are summarized in table 1, cases being listed in chronological order. The average age of the patients was 47.6 years; 9 were males, 5 were females. All had a functional capacity of class III or IV by the criteria of the New York Heart Association. The classic triad of angina, syncope, and left ventricular failure was experienced by only 1 patient. Seven patients had two of these symptoms and 6 patients noted only one. The aortic systolic murmur dominated the auscultatory findings in all cases, and a diastolic component of the aortic murmur was heard in 11 cases, diastole being silent in only three. The short early diastolic aortic murmur associated with inadequate flexibility of the leaflets and delayed valve closure was not regarded as indicative of significant coexisting aortic insufficiency. The rather longer diastolic murmur, decrescendo in character, were associated with significant aortic insufficiency in all but 1 instance. Very minor degrees of associated mitral valve disease were suggested in only 2 cases and were not believed to be of any substantial hemodynamic significance.

Electrocardiograms demonstrated changes consistent with left ventricular hypertrophy in all cases except number 2 (fig. 1, *left*), in which hypertrophy was barely suggested. In 4 instances the possible discovery of the findings usually associated with left ventricular hypertrophy was precluded by persistent complete left bundle-branch block. Careful inspection of the tracings and historical data did not indicate a postinfarctional basis for these conductional disturbances. Two patients evidenced an intraventricular block of the left bundle-branch-block configuration with a QRS duration of less than 0.12 second. This also made the strict interpretation of left ventricular hypertrophy difficult, but it was regarded as support for the diagnosis of advanced left ventricular hypertrophy. All patients had sinus rhythm, and histories consistent with paroxysmal atrial fibrillation were given by 2, of whom 1 had electrocardiographic documentation of the arrhythmia. The electrocardiogram in figure 1 (*right*) is rather typical of those encountered in this series.

Thoracic roentgenography and cardiac fluoroscopy, as adjuncts in the preoperative assessment of the patient, afforded evidence of left ventricular hypertrophy and aortic valvular calcification in every instance. The typical cardiac configuration in moderately severe aortic stenosis with a minor degree of associated aortic insufficiency and valvular calcification may be seen in figure 2. In 8 cases there was little or no cardiomegaly (table 1). The hearts of greatest size were encountered in cases in which aortic insufficiency was significant.

Findings at Operation

Pressure Measurements

Pressure gradients across the aortic valve were measured before and after repair of the valve (table 2). The systemic cardiac output was not measured at the same time, so that the data presented are less definitive and meaningful than one would desire. Mindful of this limitation, one still

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

*We extend our appreciation to Drs. F. Henry Ellis, Jr., and Dwight C. McGoon for the inclusion of cases in which they performed the operations.

may derive some appreciation of the relative severity of the disease in these patients and note that the pressure gradients were reduced by operation but not nullified. In figure 3 may be seen an example of such measurements obtained with the patient (case 5) under anesthesia and with the chest open. The systemic pressure rose simultaneously with the fall in the left ventricular pressure, suggesting that a decrease in cardiac output was not responsible for the reduction in the pressure gradient across the aortic valve.

Valve Types

In every case of this series the aortic valve was extensively, heavily calcified. In some instances the calcification extended through the leaflets into the subvalvular tissues of the outflow tract of the left ventricle. In other instances not only the leaflets were calcified but much of the adjacent aortic wall as well.

A condition justifying the designation "pure" aortic stenosis was encountered in 6 cases, the valvular orifice being so small in each that significant regurgitation through it seemed impossible. Presumably some slight degree of flexibility remained in such valves. In the other 8 cases some measure of aortic incompetence was apparent. For 4 of these, the expression "washer-type valve" conveys rather well the fact that the leaflets in this situation were rigid, forming an orifice whose size was unaltered through all phases of the cardiac cycle and thus causing significant obstruction as well as incompetence.

The valve in 4 cases seemed basically a congenitally bicuspid structure that had undergone calcification (table 2). Presumably the loss of leaflet flexibility in this process converted an originally nonobstructing valve into an obstructing lesion. It might be assumed that the rheumatic process is not required for the creation of this type of calcareous aortic stenosis.

Operative Technic

All operations in this series utilized whole-body perfusion established as described in previous reports.[3, 4] The surgical approach was through a median sternotomy incision. In most cases a catheter was placed in the left atrium for suction drainage during the period of whole-body perfusion.

After perfusion was established the aorta was cross-clamped and an incision made in the ascending portion. The heart was allowed to stop from ischemia. Ordinarily after 15 to 20 minutes of ischemia, direct perfusion of the right and left coronary arteries at a flow rate of about 400 ml. per minute has been utilized for 3 to 5 minutes, then usually discontinued and repeated after another 15 to 20 minutes of ischemia. In a few patients continuous perfusion of the left coronary artery was established. At the completion of the operative procedure upon the valve itself, the aortic incision was closed around the perfu-

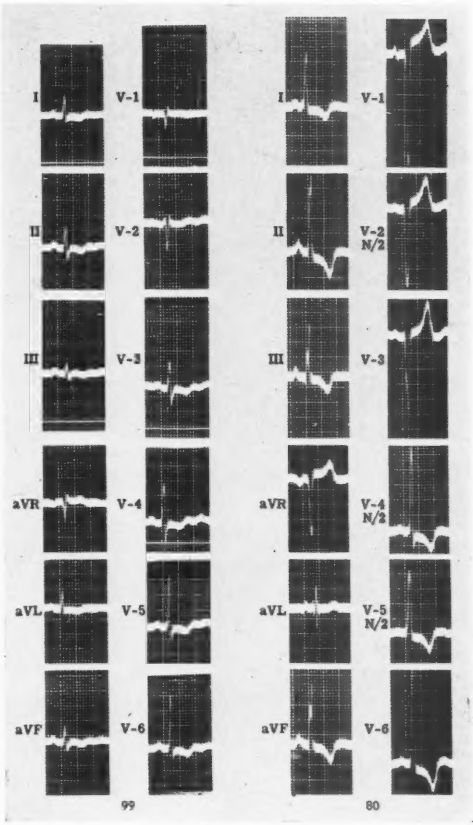

Figure 1

Case 2, left; *and case 14,* right. *Electrocardiograms in 2 patients with comparable degrees of aortic stenosis. Transaortic valve pressure gradient was 99 mm. Hg in patient represented on left (undigitalized) and 80 mm. Hg in patient represented on the right (digitalized). Degree of left ventricular hypertrophy reflected by electrocardiogram has not been a reliable index of severity of aortic stenosis at operation. Nearly normal curves may be encountered in severe stenosis, as in case 2. More typical curves are seen in tracings from case 14.*

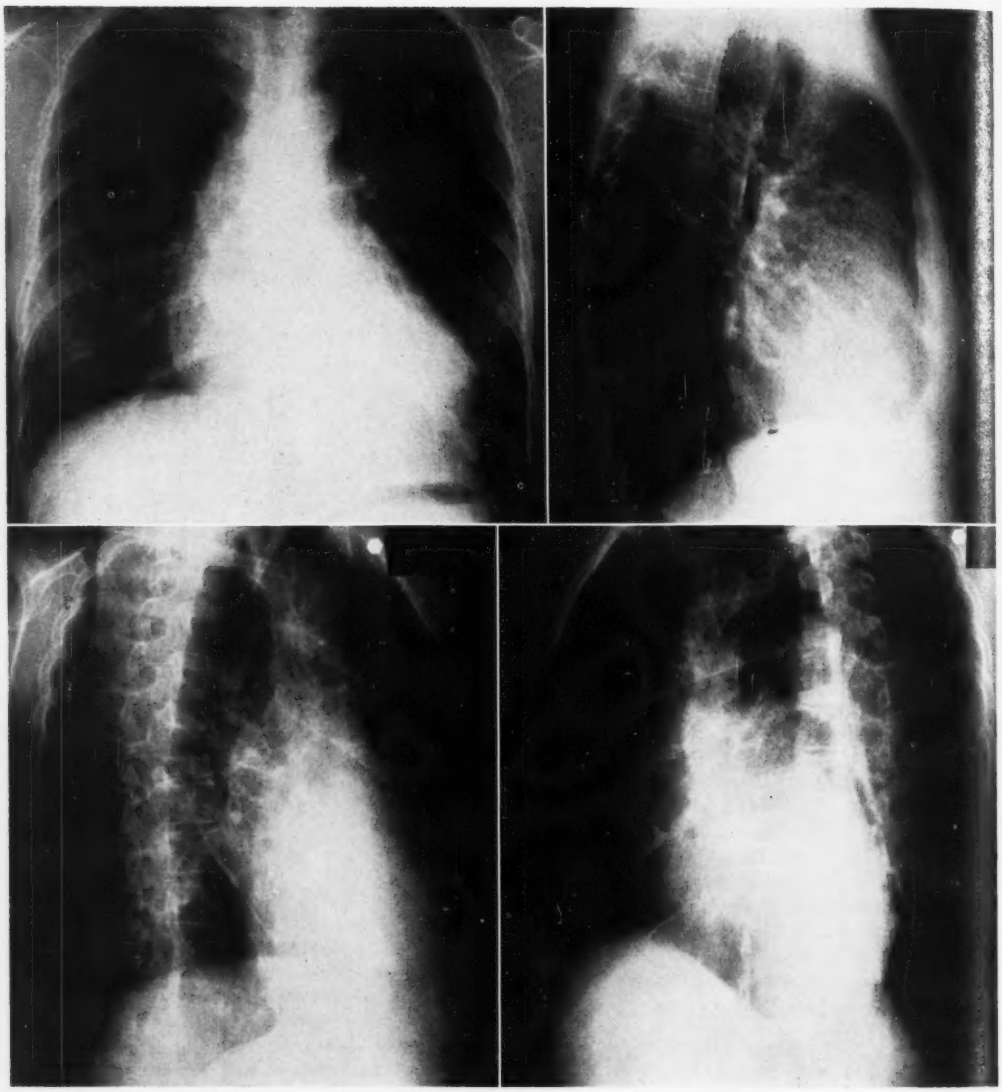

Figure 2

Case 5: upper left, *posteroanterior;* upper right, *lateral;* lower left, *right anterior oblique;* lower right, *left anterior oblique. Severe aortic stenosis with associated mild aortic insufficiency. Some appreciation of the left ventricular size may be had from the posteroanterior and left anterior oblique views. Calcification of the aortic valve is evidenced in the lateral and left anterior oblique views. These films are representative of those encountered in this series.*

sion cannulae attached to the coronary artery. When these were withdrawn, the lips of the remaining part of the incision were exteriorized by a fine-toothed Potts' clamp. Then the aortic clamp was opened. If ventricular fibrillation occurred it was treated by electrical

Table 1

Clinical Data from Fourteen Patients Who Underwent Operation by Open Technic for Calcific Aortic Stenosis

Case	Age, sex	N.Y. H.A. class	History			Murmurs*			Electrocardiographic signs			X-ray signs*		Diagnosis	
			Angina	Syncope	LVF	Aortic S	Aortic D	Mitral S or D	Rhythm	LVH	Block	Cardiomegaly	LV size	Primary	Associated
1	49, M	IV	+	0	+	3	2	D	SR	+	LBBB	3	3	AS	AI, ?MS
2	56, F	III	+	+	0	2	0	O	SR	0	0	1	1	AS	O
3	42, M	III	+	+	0	3	1	S	PAF	+	0	0	1	AS	AI, MI
4	52, M	IV	+	+	+	3	1	O	SR	+	0	1	2	AS	AI
5	49, F	III	0	0	+	4	2	O	SR	+	0	2	2	AS	AI
6	40, M	III	0	+	0	3	0	O	SR	+	0	0	1	AS	O
7	45, M	III	+	0	+	3	2	O	SR	+	LBBB	2	2	AS	AI
8	37, F	III	+	0	0	4	2	O	SR	+	IVB	2	2	AS	AI
9	47, M	III	0	+	0	2	1	O	SR	+	LBBB	1	2	AS	O
10	39, M	III	+	0	0	4	1	O	SR	+	0	1	2	AS	O
11	66, M	III	0	+	0	2	1	O	PAF	+	IVB	1	1	AS	O
12	53, M	IV	+	0	+	3	2	O	SR	+	LBBB	3	3	AS	AI
13	53, F	III	+	+	0	3	0	O	SR	+	0	1	1	AS	O
14	39, F	III	+	+	0	4	2	O	SR	+	0	2	2	AS	AI

*Graded on a basis of 0 to 4.

Abbreviations used: AI, aortic insufficiency; AS, aortic stenosis; D, diastolic; IVB, intraventricular block; LBBB, left bundle-branch block; LVF, left ventricular failure; LVH, left ventricular hypertrophy; MI, mitral insufficiency; MS, mitral stenosis; N.Y.H.A., New York Heart Association; PAF, paroxysmal atrial fibrillation; S, systolic; SR, sinus rhythm.

shock to restore a coordinated rhythm. It is not possible at this time to state whether continuous coronary artery perfusion or even intermittent coronary artery perfusion offers a significant advantage over anoxic arrest for periods up to approximately 30 minutes.

It has become apparent in this group of cases as well as in other cases that the most important factor in resuscitating the heart after operations on the aortic valve is the competence of this valve when the aortic clamp is released. No matter what method has been used to arrest the heart—be it ischemia, hypothermia, or injection of potassium—its prompt restarting can be accomplished only if effective coronary perfusion is maintained when the clamp across the ascending aorta is released. The establishment of such an effective coronary perfusion demands a competent aortic valve or some mechanical substitute therefor. If the aortic valve has been incompetent prior to operation, the restoration of its competence must be one of the primary goals of the surgical procedure.

The actual surgical measures applied to the aortic valves themselves must vary from case to case in accord with the exact anatomic situation encountered. As yet, experience is too small to allow the detailing of the operative maneuvers with confidence that they are the proper ones. Generally, however, 2 types of endeavor are made. First is a painstaking effort to restore some degree of mobility to the valve leaflets by excising the pieces of calcium that are distributed so extensively through them. Bailey[2] was the first to suggest that this could be accomplished, and our experience supports his belief that it is feasible. Care must be taken to avoid extensive damage to the leaflets in this dissection. If small rents are made in the leaflets, they can be repaired with fine silk sutures. This partial restoration of mobility to the leaflets is the most important maneuver for the treatment of any aortic valvular insufficiency that may be present with calcareous disease of the aortic valve.

Second, after mobility has been improved the commissures in the leaflets must be opened widely. If the valve was originally bicuspid it is unwise, of course, to open more than the 2 normally present commissures. In some patients, however, the valve appears to have been

Table 2

Summary of Pressure Gradients Across Aortic Valve, Valve Types, and Surgical Results from Open Operation for Calcific Aortic Stenosis

Case	Time	Direct pressure measurements, mm. Hg			Valve status*		Course		
		LV	Aorta	SG	Type	Leaflets	Follow-up, mo.	Alive	Results
1	Preop	232/5	89/44	143	Washer†	3	9	Yes	Good
	Postop	182/20	121/63	61					
2	Preop	205/8	106/74	99	Pure AS	3	9	Yes	Excellent
	Postop	146/8	98/69	48					
3	Preop	242/19	87/60	155	Washer	3	9	Yes	Excellent
	Postop	119/18	103/70	16					
4	Preop	280/20	169/87	111	Pure AS	2	7	Yes	Good
	Postop	143/7	89/69	54					
5	Preop	224/9	120/53	104	Washer	3	7	Yes	Very good
	Postop	150/9	129/70	21					
6	Preop	225/12	92/64	133	Pure AS	3	6	Yes	Good
	Postop	152/5	83/59	69					
7	Preop	190/35	120/60	70	AS, slight AI	2	6	Yes	Good 5 mo., then LVF 1 mo.: unimproved
	Postop	146/10	120/70	26					
8	Preop	245/7	131/44	114	Washer	3	7	Yes	Too early to evaluate
	Postop	156/8	112/53	44					
9	Preop	160/9	110/80	50	Pure AS	2	3	Yes	Too early to evaluate
	Postop	95/10	85/57	10					
10	Preop	251/16	131/74	120	AS, slight AI	3	2	Yes	Too early to evaluate
	Postop	127/18	92/61	35					
11	Preop	210/10	120/65	90	Pure AS	3	2	Yes	Too early to evaluate
	Postop	112/9	96/60	16					
12	Preop	211/22	100/80	111	Moderate orifice; rigid, non-fused leaflets	3	0	No	Died at operation
	Postop	—	—	—					
13	Preop	249/27	118/82	131	Severe AS	2	1	No	Died 34 days p.o. Myocardial infarction secondary to left coronary-artery dissecting aneurysm
	Postop	150/20	95/72	55					
14	Preop	200/17	120/78	80	Washer	3	1	Yes	Too early to evaluate
	Postop	140/14	100/73	40					

*All very heavily calcified.

†Term explained in text.

Abbreviations: AI, aortic insufficiency; AS, aortic stenosis; LVF, left ventricular failure; SG, systolic gradient.

tricuspid originally. In this circumstance it seems completely advisable to open all 3 commissures widely in order to establish the largest possible effective orifice. At times part of a leaflet, loosened from the aortic wall at a commissure during the opening, must be reattached to it.

Results

One patient (case 12) failed to survive the operative procedure itself. He had been in left ventricular failure rather constantly for 2 years prior to operation, and episodically for 8 years before that.

One of the 13 who left the hospital alive died later. This patient (case 13) was regarded preoperatively as being highly suitable for operative intervention. She tolerated the operative procedure well. The right coronary artery was perfused intermittently and the left coronary artery was perfused continuously while the aorta was open. During the first few postoperative days the patient complained of chest pain that could not be construed as typical angina pectoris. In retrospect it seems the pain may well have represented the discomfort of myocardial ischemia. At home, after the usual period of hospitalization, she did not experience angina on effort; but symptoms developed that were

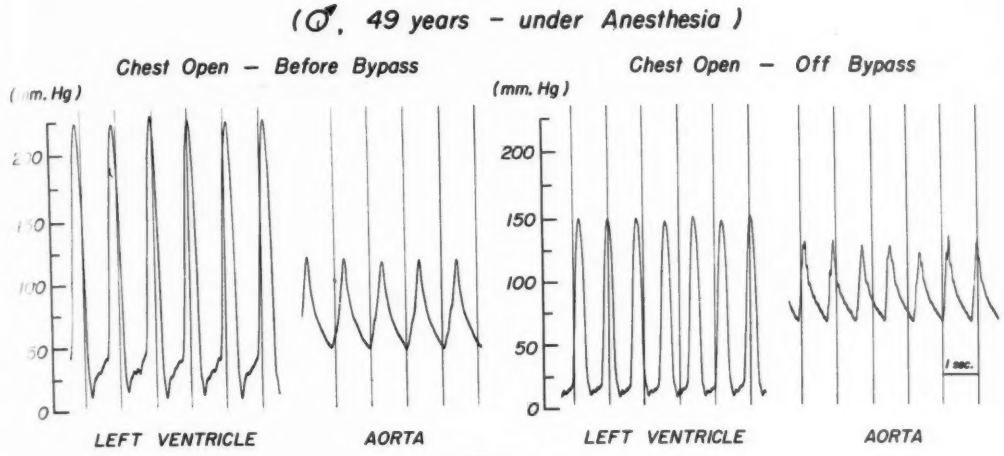

Figure 3

Case 5. Left ventricular and aortic pressures recorded during operation in a patient with calcific aortic stenosis.

consistent with left ventricular failure. She was hospitalized again, exhibiting cardiac failure not responsive to treatment and presenting the clinical appearance of reduced cardiac output. She died 34 days after operation.

Necropsy disclosed adequate surgical relief of the aortic stenosis. The lumen of the left coronary artery was narrowed by the false channel of a dissecting aneurysm. An extensive anteroseptal myocardial infarct was estimated by the pathologist to be 1 month old. The electrocardiograms recorded preoperatively and on the thirteenth postoperative day may be seen in figure 4. The postoperative loss of R wave in the electrocardiogram in V_1 and V_2 may reflect the infarction. Possibly the direct perfusion of the left coronary artery resulted somehow in trauma to the left coronary ostium, creating a dissecting aneurysm of the left coronary artery (fig. 5) and thus leading to the development of the extensive anteroseptal myocardial infarction.

Seven of the 14 cases have been followed 6 or more months, none longer than 9 months. In this short period of observation, 6 of these 7 cases appear to have good or better than good results. The seventh patient is considered unimproved by the operation; he had experienced bouts of left ventricular failure before, and he has exhibited the same tendency on one occasion since. Probably his lack of improvement reflects inadequate mechanical betterment of valve function or associated coronary artery disease, or both.

In cases followed less than 6 months, palliation cannot be evaluated fairly. It is self-evident that these and many more cases must be followed for a considerably greater period before it can be said with certainty that the natural history of the disease has been significantly altered by the operation.

Discussion

The success achieved in some cases by the closed transventricular operation for calcareous aortic stenosis, as originally employed by Bailey and associates[5] and Brock,[6] is an indication of how small an increase of the effective aortic orifice can bring about considerable clinical improvement. The perfection attained by Harken and associates[7] in the use of the transaortic technic and the careful follow-up studies of Abelmann and Ellis[8] contribute much to our knowledge and have helped stimulate further efforts in this field. Glover and Gadboys[9] have continued to be enthusiastic concerning the safety and effective palliation

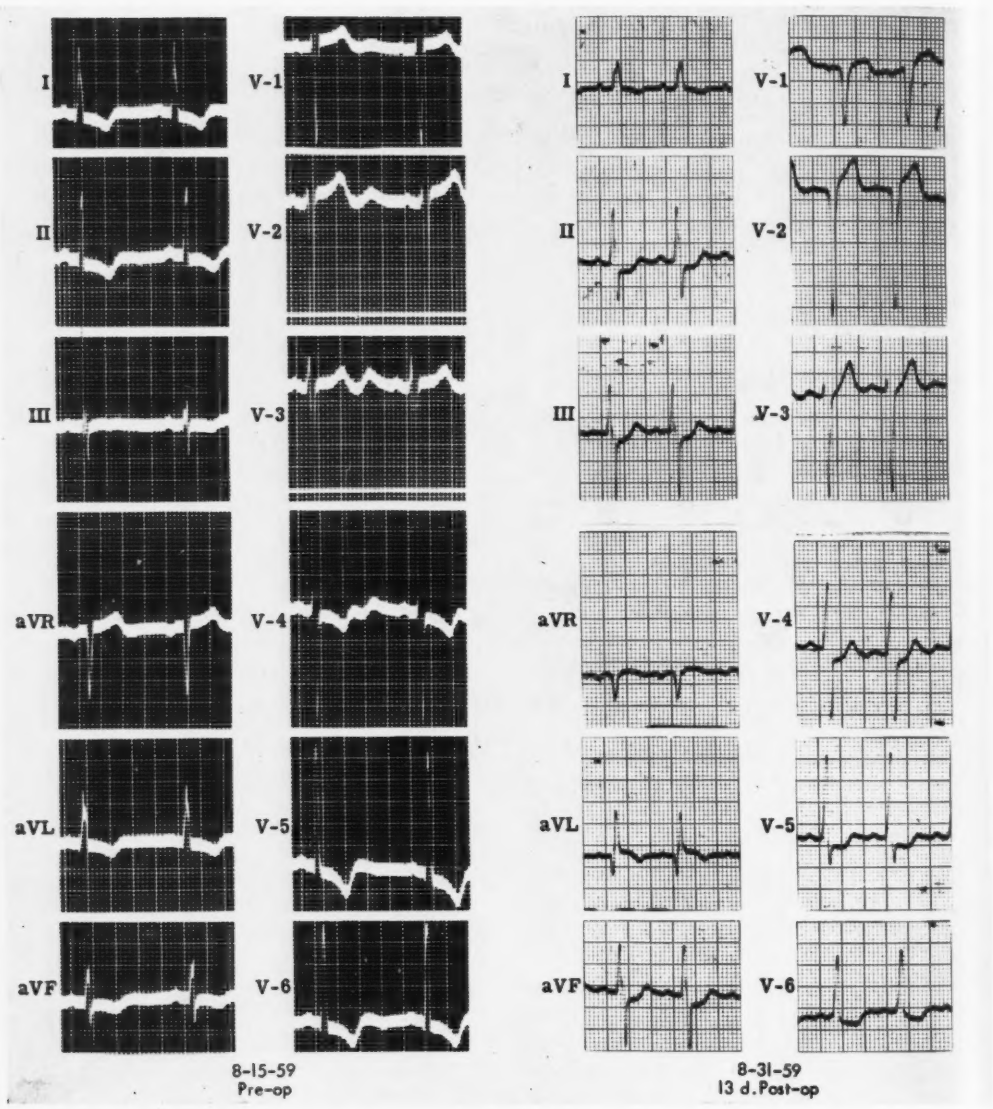

Figure 4

Case 13. Electrocardiographic tracings made 4 days before and 13 days after operation. Patient died on thirty-fourth postoperative day with an extensive anteroseptal myocardial infarction from base to apex of heart. Most aberrations evident in the second tracing are consistent with those usually seen after operation, making precise detection of a postoperative myocardial infarction difficult.

attained by the transventricular operation. The technics for open transaortic operation under hypothermia, as performed by Lewis and co-workers[10] and by Swan and Kortz,[11] have not seemed adequate for good restoration of valve function.

Gorlin and his collaborators[12, 13] have made observations pertinent to surgical treatment

of aortic stenosis in evolving a method for estimating the interrelationships of pressure gradients across the valve, aortic flow, size of the aortic valvular orifice, and left ventricular work. These data attest to the significance of a critical size of the valvular orifice at which clinical symptoms may be expected to appear. They also lend validity to the expectation that minimal enlargement of the orifice will greatly reduce the left ventricular work load. Conversely, the tremendous work expenditure required by the coexistence of aortic insufficiency with severe aortic stenosis places upon the surgeon a considerable responsibility to avoid creating or aggravating insufficiency when relieving the stenosis. In this regard closed procedures have not given consistent results, a fact responsible in part for our turning to the use of an open technic with the aid of extracorporeal circulation. The anticipated advantage was substantiated in advance by postmortem studies of the heart by Austen and associates.[14] In the laboratory they carried out a variety of operative approaches to the valve, and by perfusing the left ventricular-aortic system after the simulated operation they documented the degrees of residual hemodynamic abnormality.

The seriousness of calcareous disease of the aortic valve is well illustrated by the fact that during the 9 months covered by our study 6 additional patients scheduled for operation died suddenly and unexpectedly before the surgical date. The mean interval from evaluation for operation to death was slightly less than 3 months. All had been ambulatory and had demonstrated adequate cardiac compensation. None had intractability of symptoms and thus none had been considered emergency candidates for operation. Careful retrospective appraisal of each of these cases has not provided the desired clue to the imminence of death.

It is not suggested that the 14 cases reported prove the operation truly palliative, nor that they prove the current efforts have altered the natural history of the disease. More complete hemodynamic data, a longer period of follow-up evaluation, and a larger series of cases are required. The present small experience has indicated the feasibility of a plastic revision of the severely deformed calcareous aortic valve. In suitable cases the operative technic has been extended since October 1 by partial replacement of a cusp with a prosthesis of Teflon cloth.

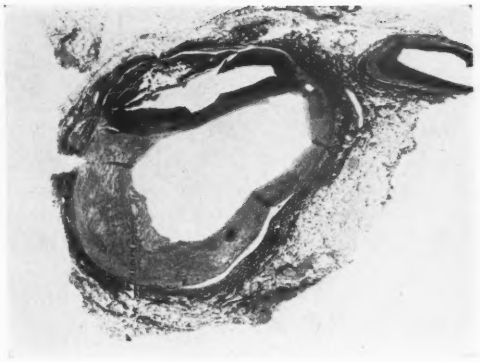

Figure 5

Case 13. Section of left coronary artery. False channel of dissecting aneurysm, visible in arterial wall, extensively involved circumflex and anterior descending arteries, resulting in anteroseptal myocardial infarction. (Hematoxylin and eosin.)

Experience in the reported series has demonstrated that the operations employed can be accomplished with reasonable hospital mortality. The incomplete hemodynamic data available suggest that improvement in valvular function has been attained. Symptomatic relief appears to have been real in 6 of the 7 patients traced 6 or more months after operation.

In view of these facts it is presently the practice at the Mayo Clinic to advise open operation for patients with calcareous disease of the aortic valve who show progressing or significant disability. The presence of associated aortic valvular insufficiency is not a contraindication to operation by present technics. Advanced degrees of disability and left ventricular failure likewise do not preclude operation, although they may result in a somewhat higher hospital mortality rate. Severe coexisting coronary artery disease would be regarded as a contraindication to surgical intervention.

Summary

Calcareous disease of the aortic valve, diagnosed by fairly uniform signs and measurements, has been treated in 14 cases at the Mayo Clinic by an open surgical technic with utilization of extracorporeal circulation. One patient died during the operation and another died after leaving the hospital. Among 7 cases followed 6 to 9 months after operation, definite symptomatic improvement has been shown in 6.

This disease is very dangerous, but a small improvement in the size of the valvular orifice can bring important benefits. The open operation is advantageous in avoidance of creating or aggravating insufficiency while relieving stenosis.

Presently this operation is advised for patients whose disability is significant or progressing. Severe coexisting coronary artery disease is a contraindication; but associated aortic valvular insufficiency, advanced degrees of disability, and left ventricular failure are not.

Summario in Interlingua

Morbo calcaree del valvula aortic, diagnosticate per satis uniforme signos e mesurationes, esseva tractate in 14 casos al Clinica Mayo per medio de un technica de chirurgia aperte, con le utilisation de circulation extracorporee. Un patiente moriva durante le operation; un secunde moriva post quitar le hospital. Inter le 7 casos que esseva tenite sub observation durante 6 a 9 menses post le operation, 6 manifestava grados definite de melioration symptomatic.

Iste morbo es periculosissime, sed un micre melioration in le dimensiones del orificio valvular pote resultar in importante beneficios. Le operation aperte es avantageose in tanto que illo non crea o non aggrava insufficientia durante le alleviamento del stenosis.

Currentemente le operation es recommendate in le caso de patientes con invaliditate de grados significative o de forma progredente. Le co-existentia de sever morbo de arteria coronari es un contra-indication. Sed le association de insufficientia del valvula aortic, de avantiate grados de invaliditate, e de disfallimento sinistro-ventricular non es contra-indicationes.

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Surgical Relief of Aortic Insufficiency by Direct Operation on the Aortic Valve

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THE TREATMENT of aortic insufficiency has presented a serious problem to both the physician and surgeon. Medical treatment generally has been unsatisfactory and, because of the mechanical nature of the defect, a surgical approach appears to offer the most promise. For this reason, extensive investigation of various methods has been undertaken. The development of the Hufnagle valve[1] was a significant advance in the evolution of methods for treatment and, in many instances, has been life-saving. It has not been entirely satisfactory, however, because the blood in the upper part of the body still remains insufficient because of the position of the valve in the descending aorta. A more direct method which obviates this difficulty is one which allows the surgeon by using the pump oxygenator to repair the deformed aortic valve or partially or totally to replace it with a prosthesis. In devising procedures to treat aortic insufficiency, it seems to us that the multiplicity of morphologic forms demands individualization of the operative procedure applicable to the specific type encountered. Moreover, cardiopulmonary bypass is considered a prerequisite. This report concerns the surgical treatment of this lesion at the University of Virginia Hospital.

In order to have a clear concept of the surgical problem, it is necessary to understand the etiology and pathogenesis of aortic insufficiency. Men are predominantly affected with this lesion in a ratio of approximately 3 to 1. Rheumatic fever is the most common cause, and syphilis is reported as second but was not a causative factor in our series of patients. Subacute bacterial endocarditis accounts for a significant number, and 2 of our patients had free aortic regurgitation as a result of this lesion. Two also had aortic insufficiency as a result of dissecting aneurysms of the aorta. Aortic insufficiency may be congenital. It may also be associated with Marfan's syndrome and accompanied by aneurysmal dilatation of the ascending aorta and of the aortic annulus. In addition, blunt or penetrating trauma has been reported as an etiologic agent.

Segal et al.[2] outlined the natural history of the disease in a clinical study of 100 cases and found that most patients had rheumatic fever at the age of about 13. Seven symptom-free years usually passed before hemodynamically significant aortic insufficiency occurred. Another interval followed without symptoms for about 10 years, when dyspnea, angina pectoris, and congestive failure appeared and slowly progressed for about 6½ years until death resulted suddenly from ventricular fibrillation, congestive failure, bacterial endocarditis, or coronary insufficiency. This course, though average, may be altered in many ways. All of the patients in Segal's study who followed this pattern had severe aortic insufficiency. Many patients with mild to moderate insufficiency, however, may be asymptomatic for a much longer period and may not develop significant symptoms until late in life.

Aortic insufficiency increases tremendously the work load of the left ventricle, which becomes thickened and dilated. This hypertrophy compounds the problem of inadequate blood supply to the coronary arteries because diastolic filling of these arteries is already diminished, and increased size of the left ven-

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tricular mass causes relative coronary insufficiency. This insufficiency probably accounts for the angina associated with advanced aortic insufficiency and enhances the development of cardiac failure or sudden acute ventricular fibrillation, which so often results in death.

The death of so many patients in the fourth or fifth decades makes the development of satisfactory corrective procedures of utmost importance. As mentioned previously, the most widely used surgical method of treating aortic insufficiency has been the insertion of the Hufnagel ball-valve.[3] This method is thought by its originator to control approximately 75 per cent of the reflux and thus greatly relieves the work load on the heart. The valve can be inserted rapidly into the descending aorta, but efforts in the experimental laboratory to insert it more proximally were met with complex problems. It has been pointed out that, after insertion of the Hufnagel valve, the fall of diastolic pressure in the upper extremities may result in increased angina. Moreover, the degree of clinical success has been limited in the hands of many surgeons.

Bailey[4] utilized a heavy ligature about the base of the aorta proximal to the coronary arteries to narrow the annulus and thus reduce the insufficiency, but this method proved unsatisfactory and was not employed extensively. More recently Taylor and associates[5] reported a similar procedure in 11 patients in whom there were 4 operative deaths and 2 late deaths. The other 5 patients were improved at the time of the report. In 1958 Lillehei et al.[6] reported their experience with 3 patients, 2 of whom had aortic insufficiency. The third patient developed considerable aortic insufficiency after aortic valvulotomy for stenosis. In the first 2 patients, one commissure was closed with mattress sutures to form a biscuspid valve; 1 patient survived and showed improvement. In the patient who developed insufficiency after valvulotomy one commissure was sutured but the insufficiency persisted. When the aorta was reopened, the insufficiency was found to result from inadequate coaptation of the leaflets. The suture of a small piece of Ivalon to the inadequate leaflet resulted in complete disappearance of the diastolic thrill but the patient died 2 days later.

In 1957 Wible et al.[7] described a prosthesis made from a spring covered with Nylon fabric, which was placed over the top of the insufficient valve to close the defect during diastole. This prosthesis was inserted in animals that were observed over a 20-month period with encouraging results. Roe and coworkers[8] have also reported experiments with a molded monomolecular silicone subcoronary aortic valve. Neither of these valves has been used clinically. More recently Garmella and associates[9] reported the treatment of experimentally induced aortic insufficiency by excision of the posterior leaflet and the creation of a bicuspid valve. Initial results were poor, but, in later experiments, careful coaptation of the newly formed commissure resulted in no significant degree of aortic stenosis or insufficiency in the surviving animals. Numerous other experimental methods, including transplantation of the homologous aortic valve, pericardial pedicles, vein grafts, and injection of sclerosing solutions around the valve, have proved unsatisfactory.

Operative Procedures

In our clinic, the pump oxygenator has been used at every operation for aortic insufficiency but each procedure has been modified to suit the particular type of deformity encountered. The initial portion of the operation was essentially the same regardless of the anatomic configuration of the lesion.

The patient was placed in a supine position and the right external iliac and common femoral arteries and the heart and ascending aorta were exposed through inguinal and median sternotomy incisions. Heparin, 1.5 mg. per Kg. of body weight, was administered, and the right common femoral artery and the superior and inferior venae cavae were cannulated. The perfusion was begun, and the aorta was clamped immediately proximal to the innominate artery. A longitudinal incision was made in the aorta beginning anteriorly 1

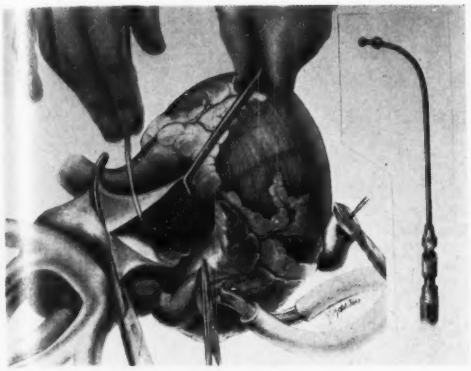

Figure 1

Perfusion of left coronary artery. Insert shows perfusion cannula.

cm. proximal to the clamp and extending inferiorly and to the right, so that it ended just above the midportion of the posterior leaflet.

Of paramount importance is coronary artery perfusion (fig. 1). We initially attempted to perfuse both coronary arteries but, because of the relatively small field and certain technical difficulties, perfusion of the left coronary artery was considered and found adequate. A quarter-inch Tygon tubing connected the arterial perfusion line to a cannula fashioned from a malleable silver laryngeal anesthesia cannula by placing an 8-mm. metal ball 8 mm. from its tip to limit introduction into the left coronary orifice. Flows measured from this cannula have varied from 240 to 450 ml. per minute, depending upon the rate of perfusion. Although ventricular fibrillation occurred in some instances during and after closure of the aorta, it has always been easily reversed with electric countershock defibrillation.

The procedures for repair according to various types of aortic insufficiency are as follows:

Rheumatic Calcific Insufficiency

This type, accompanied by some degree of stenosis, is very common. Frequently incision of the commissures alone relieved the stenosis and greatly reduced the insufficiency. When calcification was severe, excision of as much

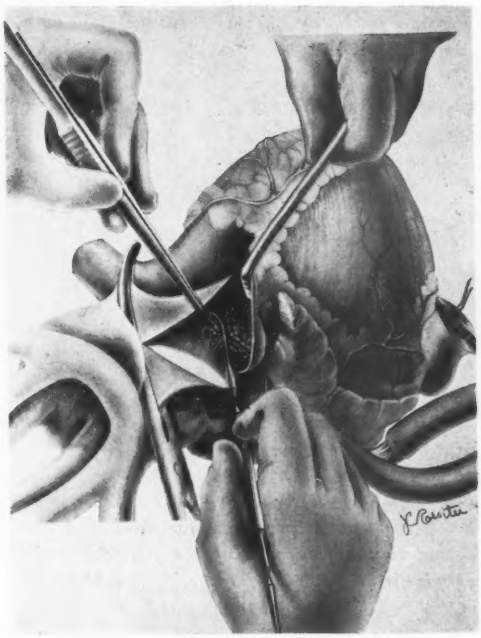

Figure 2

Removal of calcium deposits from aortic valve leaflets. A plane has been developed between the calcium plaque and the leaflet.

calcium as possible often resulted in much thinner, more supple valve leaflets (fig. 2). Occasionally a plane of separation was found that facilitated removal of the calcium deposits. In our experience, however, this plane has been uncommon. In some instances only a small central opening remained after the calcium had been excised. Then the free edge of one of the leaflets was extended with a small piece of compressed polyvinyl sponge (fig. 3). This was most easily achieved by splitting the sponge along one side, so that the free edge of the leaflet could be inserted between the 2 edges of the sponge and secured in place with interrupted sutures. The sponge may also be molded in this configuration. The distal end of the sponge should be tailored so that it overlaps the leaflets.

Often there was massive calcific replacement of the valve leaflets, which prevented calcium removal or resulted in destruction of the leaf-

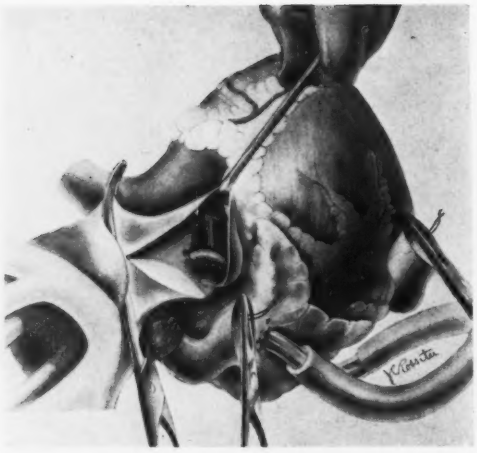

Figure 3

Correction of aortic insufficiency by a leaflet-extension procedure. A prosthetic extension has been sutured to the free edge of the posterior aortic valve leaflet.

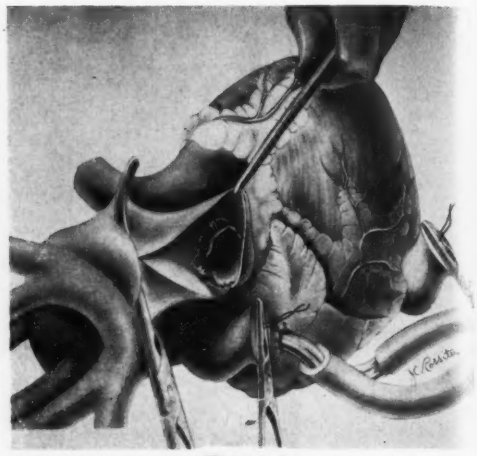

Figure 4

Approximately one half of the deformed calcified aortic valve has been removed and a prosthetic leaflet has been sutured to the annulus to fill the defect. The cusp-like configuration of the normal valve leaflet is reproduced.

let when removal was attempted. When this occurred, we excised a portion of the valve and inserted a large prosthetic leaflet tailored initially from highly compressed polyvinyl sponge, but more recently from Teflon fabric (fig. 4). The leaflet should be somewhat redundant in the transverse direction and should be long enough to overlap the remaining leaflet or portion of the leaflet by 0.5 to 1 cm. The prosthesis was sutured to the annulus with interrupted silk or Dacron sutures so as to form a deep cusp. This cusping effect was necessary to prevent regurgitation of the leaflet into the left ventricular cavity with diastole. Care should be taken to prevent its covering either coronary orifice during diastole.

Isolated Rheumatic Aortic Insufficiency

This type of disease is usually associated with little or no calcification, and 1 of 2 procedures may be used to correct it.

1. The commissures adjacent to the posterior cusp should be incised and the annulus narrowed with mattress sutures, if the annulus is only slightly dilated and if there is only moderate retraction of the valve leaflets. Incisions are made through the commissures adjacent to the posterior leaflet and into the annulus. Mattress sutures of heavy silk or Dacron should enter the aortic wall approximately 8 mm. from the commissure and emerge an equal distance from the commissure in the other sinus. When tied in place, these sutures invaginate the annulus and aortic wall and reduce its circumference (fig. 5). The commissures should be carefully coapted at their origin by placing 1 or 2 mattress sutures near the free edge of the valve leaflets. Care should also be taken to close completely the incision in the aortic wall to prevent leakage of blood after the heart is started.

2. The posterior valve cusp is removed when there is marked annular dilatation and retraction of the valve leaflets. The arteriotomy is extended down to the base of the sinus and the annulus and aortic wall are excised to within approximately 3 mm. of the commissures. Mattress sutures are placed along the edges beginning at the lower pole of the incision and tied in place, thus abutting the posterior borders of the right and left valve leaflets to form a new posterior commi-

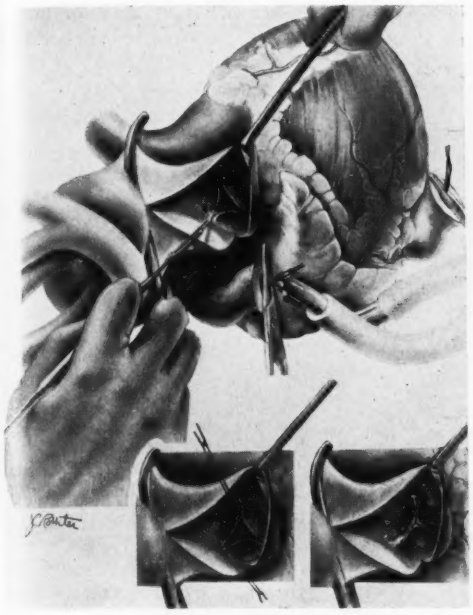

Figure 5

Annulus-constricting procedure to relieve aortic insufficiency. The annulus is incised at the commissures. Inserts show mattress sutures placed so that the annulus is constricted to approximate the valve leaflets.

sure (fig. 6). Accurate approximation of the leaflets of this commissure is imperative to prevent regurgitation. In our experience, there has been no regurgitation after creation of a bicuspid valve.

Insufficiency Resulting from Bacterial Endocarditis

Subacute bacterial endocarditis usually produces punctate holes or destroys the free edge of one or more leaflets so that improper abutment results in severe insufficiency. When the former occurs, simple closure of the opening with mattress sutures suffices (fig. 7). When the valve cusps are destroyed, complete replacement of the valve is necessary. In 1 patient, an attempt to replace only 1 leaflet resulted in destruction of the other 2 relatively normal leaflets, possibly by the prosthesis. At a subsequent operation, it was necessary to place another leaflet of compressed polyvinyl sponge opposite the one

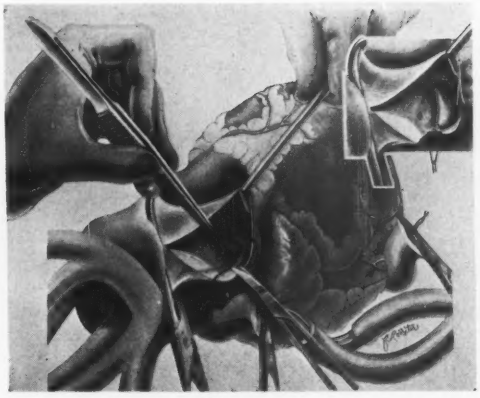

Figure 6

Creation of a bicuspid aortic valve. The posterior valve leaflet, wall of aorta, and portion of annulus are excised. Insert shows approximation of the posterior aspects of the right and left leaflets to create a bicuspid valve.

previously inserted to create a subcoronary bicuspid prosthetic valve (fig. 8). These leaflets were secured in a cusp-like fashion along the annulus with interrupted sutures. Both leaflets were redundant longitudinally and were sutured at the commissure to prevent invagination into the right ventricle during diastole. The index finger fitted loosely in the valve opening and the size was therefore thought adequate.

Marfan's Syndrome

In this syndrome, dilatation of the ascending aorta and valve ring results in insufficiency. Treatment of the valve by posterior leaflet excision and formation of a bicuspid aortic valve is the procedure of choice. The aorta should be completely freed from the pulmonary artery and, after excision of redundant aortic wall and closure of the aortotomy, it should be supported with an encircling band of Dacron or Teflon fabric to prevent future dilatation. On occasion a bicuspid valve may be present in Marfan's syndrome and one or both commissures may be incomplete or cleft. The incomplete commissure should be opened to the annulus and the cleft should be closed by an annular constricting procedure.

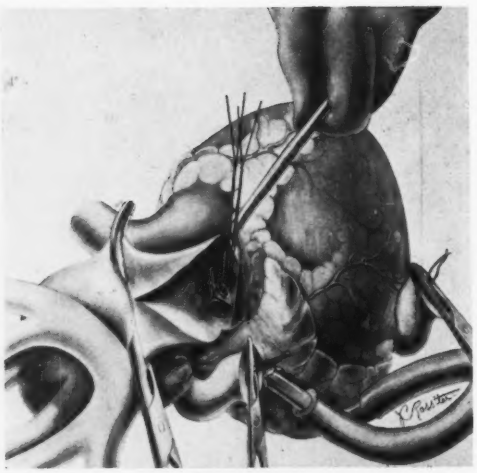

Figure 7

Method of repairing valve leaflets perforated by subacute bacterial endocarditis. Mattress sutures are placed across the perforations to close them.

Chronic Dissecting Aneurysm of the Aorta and Aortic Insufficiency

This type of insufficiency is characterized by a circumferential tear in the intima of the ascending aorta approximately 2 to 4 cm. above the aortic valve and was encountered in 2 cases, one of which was associated with Marfan's syndrome. Dissection proximally beneath the valve had occurred and an endothelial lining had developed. The valve partially invaginated into the left ventricular chamber with each diastole thus producing severe insufficiency. In order to correct this type of deformity, the aneurysm must be excised. Usually, it cannot be completely excised and the short remaining dissection proximally can be closed by including both layers in the anastomosis to a finely woven Teflon prosthesis to re-establish aortic continuity. An annulus-narrowing procedure is necessary to relieve the insufficiency and the formation of a bicuspid valve is preferred.

Selection of Patients

For the selection of patients for operation, the following criteria have been used to substantiate the diagnosis of aortic insufficiency: (1) a loud, blowing aortic diastolic murmur usually transmitted along the left sternal border toward the apex; (2) a low diastolic pressure with or without an increased systolic pressure and a wide pulse pressure; (3) peripheral findings including DeMusset's sign of systolic bobbing of the head; (4) roentgenologic evidence of cardiac enlargement, a swinging movement of the heart, and excessive pulsations of the ascending aorta; (5) an elevated end-diastolic left ventricular pressure on left heart catheterization; and (6) insufficient valve demonstrated by arterial tracings. While these findings have been present in most patients, some did not have all, but exhibited significant evidence to make a diagnosis of severe aortic insufficiency. Other findings that could not be used to differentiate insufficiency from stenosis included exertional dyspnea, angina pectoris, congestive heart failure, and electrocardiographic evidence of left ventricular strain and enlargement.

Analysis of Cases

A total of 19 patients underwent 21 operations for the correction of aortic insufficiency (table 1). There were 15 men and 4 women whose ages ranged from 18 to 61 years. The valvular deformity in 14 patients resulted from rheumatic fever.

Four patients had pure aortic insufficiency with relatively normal-appearing valve leaflets at operation. One patient (no. 1) had an annular constriction procedure and the insufficiency was completely relieved. Of 2 who had a bicuspid valve created, one (no. 2) was completely relieved and the other (no. 3) died on the second postoperative day of ventricular fibrillation. Another (no. 4) initially had a leaflet-extension procedure with a compressed polyvinyl prosthesis. This patient had a relatively small aortic annulus, and for this reason it was feared that aortic stenosis would result if a bicuspid procedure were performed. The insufficiency was not satisfactorily relieved, and 3 months later the valve was re-explored. The prosthesis was removed intact and an annulus-constricting procedure was performed. Because the insufficiency was not relieved, the aorta was re-entered and a bicuspid valve was formed, which completely re-

lieved the insufficiency. This patient's course was satisfactory until the second postoperative day, when he developed sudden cardiac arrest and damage of the central nervous system. He died 36 hours later.

Six patients had aortic stenosis and insufficiency or developed severe insufficiency after a stenotic valve was opened. In 1 of these (no. 5), a leaflet-extension procedure was performed after completion of the valvulotomy. This patient has angina on exertion possibly related to coronary artery disease but otherwise has a fair result. Two patients with stenosis and insufficiency had aortic valvulotomies and excision of calcific plaques from the valve leaflets. One patient (no. 6) died during the operative procedure of left ventricular failure; the other (no. 7) is asymptomatic and is normal hemodynamically. Three others had excision of a portion of the valve and insertion of a prosthesis. In 2 of these patients, highly compressed polyvinyl sponge was used. One (no. 8) is well and asymptomatic; the other (no. 9) died of an overwhelming mediastinal infection and septicemia. A transventricular valvulotomy had been performed 4 years ago on the third patient (no. 10), who developed subacute bacterial endocarditis 9 months later. At the second operation, approximately two thirds of the deformed calcified valve was excised and replaced with a Teflon valve leaflet (fig. 9). This patient had a lower nephron syndrome but is doing well at the present time. His stenosis and insufficiency are completely relieved.

Four patients had aortic stenosis and insufficiency complicated by significant involvement of the mitral valve. In 2 of these (nos. 11 and 12), mitral and aortic valvulotomies were performed, and calcium was removed from the aortic valves. Both have achieved excellent improvement. In 1 of the remaining 2 mitral and aortic valvulotomies were performed, and a leaflet-extension procedure with compressed polyvinyl sponge was used. In 1 (no. 13), the aortic insufficiency was relieved but a period of hypotension after the perfusion resulted in irreversible central nervous

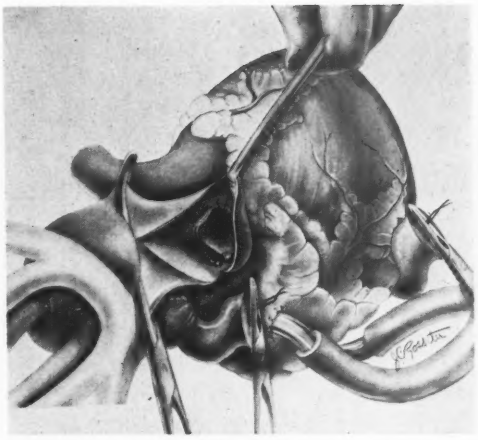

Figure 8

Complete subcoronary replacement of the aortic valve. A bicuspid prosthetic valve has been formed by 2 leaflets sutured to the aortic annulus.

system damage, and death ensued 2 days after the operation. The other (no. 14) had severe congestive failure with mitral and aortic stenosis and insufficiency and marked tricuspid regurgitation. In addition to a mitral valvulotomy and aortic valvulotomy, an annulus-constricting procedure was performed on the aortic valve. Mitral insufficiency was still present to such an extent that a plastic reparative procedure was performed on the mitral valve but the patient died toward the end of this operation.

Two patients had severe aortic insufficiency as a result of subacute bacterial endocarditis. The first (no. 15) was found to have a bicuspid valve with 2 perforations, each approximately 6 mm. in diameter, in one leaflet and one perforation, approximately 8 mm. in diameter, in the other leaflet. The 2 smaller perforations were closed with mattress sutures, and the larger perforation was reinforced with a Teflon fabric prosthesis placed on the aortic side of the valve. The insufficiency, although not completely relieved, was considerably improved. The patient seemed to progress satisfactorily but died suddenly on the fifth day probably because of ventricular fibrillation. Another patient (no. 16) had subacute bacterial endocarditis 6 months

Analysis of Cases

Table 1

Case, Sex, Age, Date	Lesion	Procedure	Perfusion time	Left coronary perfusion	Results and remarks
Group 1. Aortic insufficiency secondary to rheumatic fever					
1. OS, M, 42 5-20-59	Aortic insufficiency; dilated annulus; slightly thickened leaflets	Annulus constriction at posterior commissures	48 min.	Yes	Excellent; insufficiency completely relieved
2. DH, M, 35 5-5-59	Aortic insufficiency; dilated annulus, leaflets only slightly thickened	Creation of bicuspid valve	40 min.	Yes	Excellent; insufficiency completely relieved
3. JH, M, 45 5-6-59	Aortic insufficiency; dilated annulus; only slightly thickened leaflets	Creation of bicuspid valve	1 hr. 15 min.	Yes	Insufficiency completely relieved; died suddenly 2nd postoperative day of ventricular fibrillation
4. RM, M, 50 4-30-59 7-16-59	Retracted right leaflet, relatively normal appearing valve	(1) Ivalon extension of right leaflet (2) Removal Ivalon extension, creation of bicuspid valve	(1) 46 min. (2) 1 hr. 40 min.	Yes, both procedures	1. Considerable insufficiency still present 2. Insufficiency completely relieved; died 3rd postoperative day following acute ventricular fibrillation and central nervous system damage
5. RB, M, 43 6-5-58	Calcific aortic stenosis and aortic insufficiency	Valvulotomy, Ivalon leaflet extension	30 min.	No	Good, has had angina recently
6. PK, M, 51 6-23-59	Aortic insufficiency and aortic stenosis, calcific	Valvulotomy, excision of calcium from valve leaflets	1 hr. 50 min.	Yes	Died during operation of severe left ventricular failure
7. EB, M, 43 7-2-59	Calcific aortic stenosis and aortic insufficiency	Valvulotomy, excision of calcium from valve leaflets	30 min.	Yes	Excellent
8. JP, M, 53 11-26-58	Severe calcific aortic stenosis	Valvulotomy, excision of valve leaflet; replacement with Ivalon valve leaflet	1 hr. 9 min.	Yes	Excellent; all symptoms relieved to present
9. PL, M, 38 3-25-59	Severe calcific aortic stenosis	Valvulotomy, excision of ½ valve; replacement with Ivalon valve leaflet	53 min.	Yes	Died 32 days postoperatively from midcolonal infection and septicemia
10. CO, M, 47 7-8-59	Aortic stenosis and aortic insufficiency, calcific	Resection 2/3 valve; insertion Teflon valve leaflet	1 hr. 8 min.	Yes	Transventricular valvulotomy, 1946, and subsequent subacute bacterial endocarditis. Aortic stenosis and aortic insufficiency completely relieved; transient lower nephron syndrome
11. HJ, M, 31 6-26-59	Aortic insufficiency, aortic stenosis, calcific; mitral stenosis and mitral insufficiency	Aortic valvulotomy, excision of calcium from leaflets, mitral valvulotomy	48 min.	Yes	Excellent; aortic insufficiency and aortic stenosis relieved. Still has minimal mitral insufficiency
12. EH, F, 45 12-4-58	Calcific aortic stenosis and aortic insufficiency; mitral stenosis and mitral insufficiency	Aortic and mitral valvulotomy; excision calcium from aortic valve	38 min.	Yes	Excellent, asymptomatic
13. FV, M, 37 1-7-59	Calcific aortic stenosis and aortic insufficiency; mitral stenosis and mitral insufficiency	Aortic and mitral valvulotomies; Ivalon extension of posterior leaflet	1 hr. 35 min.	Yes	Stenosis and insufficiency completely relieved; Died of central nervous system damage following period of hypotension
14. MM, F, 18 6-30-59	Aortic insufficiency and aortic stenosis; mitral insufficiency and stenosis; tricuspid insufficiency	Aortic valvulotomy, annulus constriction, mitral valvulotomy; Repair of insufficiency of mitral valve	2 hrs. 20 min.	Yes	Died shortly after operation of severe congestive failure

Table 1 (cont'd)

Group 2. Aortic insufficiency secondary to subacute bacterial endocarditis						
15.	GC, M, 28 10-21-58	Three perforations of the bicuspid valve	Closure of perforations; Teflon reinforcement of valve leaflet	1 hr. 33 min.	Yes	Died 5th postoperative day probably of acute ventricular fibrillation
16.	LW, F, 34 12-17-58 1-6-59	Perforation of left leaflet Destruction of right leaflet	1. Excision, right leaflet, insertion Ivalon prosthesis; closure of perforation; 2. Excision, right and posterior leaflets; insertion Ivalon prosthetic subcoronary valve replacement	(1) 1 hr. 32 min. (2) 2 hr. 7 min.	Yes, both procedures	1st operation—insufficiency initially relieved but returned; 2nd operation—excellent; insufficiency completely relieved; mild aortic stenosis
Group 3. Marfan's syndrome or dissecting aneurysm, or both						
17.	CT, M, 61 12-6-58	Dissecting aneurysm and aortic insufficiency	Resection dissecting aneurysm of ascending aorta; insertion Dacron prosthesis	1 hr. 38 min.	Yes	Insufficiency partially relieved; died due to uncontrollable bleeding through prosthesis
18.	AF, F, 38 7-7-59	Marfan's syndrome, dissecting aneurysm; circumferential intimal tear, aortic insufficiency	Resection dissecting aneurysm of ascending aorta; insertion Teflon prosthesis; creation of bicuspid valve	2 hrs. 45 min.	Yes	Excellent, aortic insufficiency completely relieved
19.	WW, M, 18 5-1-59	Marfan's syndrome; cleft bicuspid valve; questionably congenital	Aortic valvulotomy; constriction of annulus and closure of cleft; fabric support of ascending aorta	1 hr. 29 min.	Yes	Excellent, aortic insufficiency completely relieved

previously, with destruction of the free edge and medial one third of the right leaflet. A perforation in the left leaflet approximately 5 mm. in diameter was closed with a silk mattress suture; the destroyed leaflet was excised, and compressed polyvinyl leaflet was inserted along the area of excision. The insufficiency was completely relieved but, at the end of 24 hours, gradually recurred and became severe. After 3 weeks of continued deterioration, the valve was again explored and the remaining 2 leaflets were found to be partially destroyed. Repair was unsuccessful and these leaflets were excised and a second compressed polyvinyl sponge leaflet was inserted to form a bicuspid prosthetic valve. A superficial wound infection, which developed in the median sternotomy, cleared without incident. The patient is asymptomatic and has an excellent result. Postoperative left ventricular catheterization demonstrates a mild degree of aortic stenosis, which appears to be insignificant, but no insufficiency is present.

Three patients with severe aortic insufficiency had dilatation of the ascending aorta, and 2 of them had dissecting aneurysms and circumferential rupture of the intima 3 cm. above the aortic valve. The proximal dissection to the aortic valve caused the valve to invaginate with each diastole. One patient (no. 17), who had excision of the aneurysm and insertion of a Dacron prosthesis, died because of continued bleeding through the prosthesis. The other (no. 18) with Marfan's syndrome had excision of the dissecting aneurysm and Teflon prosthetic replacement of the aortic segment. A bicuspid valve was also created, which relieved the aortic insufficiency. The patient with Marfan's disease and a congenital bicuspid valve (no. 19) underwent annulus constriction and repair of 1 cleft commissure. The excessive aortic wall was excised, and the ascending aorta was encircled with a supporting fabric prosthetic band.

At present 11 of these 19 patients are well or markedly improved. The mortality rate appears high but all of these patients had severe valvular disease and a number had multivalvular disease. In addition, all had

Figure 9

Photograph of partial replacement of stenotic and insufficient aortic valve on patient no. 10 (C.O.). Sutures have been placed in the annulus and along the edge of a Teflon fabric prosthesis, which has not yet been tailored to fit the configuration of the remaining valve.

been in congestive heart failure or were in failure at the time of operation. Several had significant sclerosis of the coronary artery as well. Experience with these patients brought forth information that we believe will offer a progressively improving mortality rate. First of all, the selection of patients is of utmost importance. The type of patient such as (no. 3), who had severe cardiac enlargement and congestive failure and an extremely low myocardial reserve, will present a much greater risk than one whose disease is not so far advanced. Multivalvular lesions, especially mitral insufficiency in association with aortic insufficiency will also greatly increase the risk and reduce the chance of benefit. For the patient with noncalcific isolated aortic insufficiency, a procedure to reduce the size of the annulus and to allow coaptation of the valve leaflets is the only one that will relieve the insufficiency other than complete valve replacement. If the annulus is small, we have used the annulus-constricting operation; if it is large, the formation of a bicuspid valve is satisfactory and will completely relieve the insufficiency.

When severe calcific stenosis and insufficiency are present, an annulus-constricting procedure is not satisfactory. A complete valvulotomy should first be performed, with removal of as much calcium as possible, and every effort should be made to utilize the patient's own tissues. When this cannot be done, a synthetic prosthesis may be used. Some of the new synthetic materials, such as Teflon, have great tensile strength, do not deteriorate when implanted in living tissues, and can withstand great wear. One must also remember that such a prosthesis is well lubricated by the stream of blood, and this reduces wear. It is of utmost importance that the prosthesis be placed so that the cusp-like configuration of the normal valve leaflet is retained, for this is perhaps the most important factor in preventing regurgitation of the leaflet into the left ventricle. It should also be broad enough to allow adequate opening and should overlap the remaining valve tissue centrally about 0.5 cm. That total prosthetic valve replacement is possible has been demonstrated by the patient whose valve continues to function satisfactorily 10 months after operation. It is entirely probable that extremely calcified or deformed aortic valves will be replaced as better artificial valves, which may be expected to last a normal lifetime, are developed.

Of considerable interest is speculation as to whether or not a prosthesis will develop an infection when placed in an area where bacterial valvulitis has been present. In our 3 patients who had subacute bacterial endocarditis, 1 did not live sufficiently long for evaluation but there is no evidence of an infection on these foreign bodies in the other 2, one having been observed for 10 months.

We are convinced that a direct attack upon the insufficient aortic valve is the procedure of choice at the present time with the goal of totally correcting aortic insufficiency. With further experience and investigation, it is probable that more satisfactory methods will evolve with an accompanying lower mortality rate.

Summary

The natural history of patients with aortic insufficiency and the previous experimental and clinical operations devised for its relief are reviewed.

Methods that have been used at the University of Virginia Hospital for treatment of aortic insufficiency are reported. These procedures include the release of the fixed valve leaflet and removal of calcium from it, aortic valve leaflet extension with suture of a small piece of compressed polyvinyl sponge or Teflon fabric to the edge of one of the leaflets, excision and replacement of a portion of the valve with a synthetic leaflet, and complete subcoronary replacement of the valve with a prosthesis. To relieve isolated rheumatic aortic insufficiency, an annulus has been constricted or a bicuspid aortic valve has been created. Insufficiency resulting from perforation of one or more valve leaflets by subacute bacterial endocarditis has been treated by closure of the perforations.

Nineteen patients underwent 21 operations for the correction of aortic insufficiency. All had been in, or were in, heart failure, and several had significant coronary artery disease or multivalvular disease. Eleven of the 19 patients are well or markedly improved. Eight died during or after the operative procedure.

It is concluded that a direct attack upon the insufficient aortic valve is the procedure of choice at the present time.

Summario in Interlingua

Es presentate un revista del historia natural de patientes con insufficientia aortic e del operationes elaborate experimentalmente e applicate clinicamente pro su alleviamente usque al tempore presente.

Es reportate le methodos usate al Hospital del Universitate Virginia in le tractomento de insufficientia aortic. Iste methodos include le liberation de fixate segmentos valvular e le elimination de calcium ab illos, le extension de un segmento del valvula aortic per medio del sutura de un micre pecia de comprimite spongia de polyvinyl o de Teflon contra le margine de illo, le excision de un portion del valvula e su reimplaciamento per un segmento synthetic, e le complete reimplaciamento subcoronari del valvula per un prosthese. Pro alleviar isolate insufficientia rheumatic del valvula aortic, un anulo has essite constringite o un bicuspidic valvula aortic ha essite create. Insufficientia resultante ab le perforation de un o plures del segmentos valvular per subacute endocarditis bacterial ha essite tractate per clauder le perforationes.

Dece-novem personas esseva operate pro le correction de insufficientia aortic. Omnes habeva essite o esseva in discompensation cardiac, e plures habeva grados significative de morbo del arteria coronari o de morbo multivalvular. Dece-un del 19 patientes se trova ben o marcatemente meliorate. Octo moriva durante o post le intervention operatori.

Es concludite que le attacco directe super le insufficiente valvula aortic es le operation de election al tempore presente.

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CLINICAL PROGRESS

Antibody Titers in Acute Rheumatic Fever

By LEWIS W. WANNAMAKER, M.D., AND ELIA M. AYOUB, M.D.

THE INDISTINCT boundaries of the clinical picture of rheumatic fever and the lack of a specific diagnostic test have led to the formulation of an arbitrary list of criteria for the diagnosis of the acute disease[1] and to the use of laboratory aids that are nonspecific but nevertheless informative.

The laboratory tests used in rheumatic fever fall into 2 general groups, (1) the acute phase reactants and (2) bacteriologic and immunologic studies confirmatory of a preceding streptococcal infection. Each of these groups yields information relevant to a different facet of the disease process. None of the tests in either group is diagnostic of rheumatic fever.

The *acute phase reactants*, which include the erythrocyte sedimentation rate, the C-reactive protein, and the serum mucoprotein determinations, are positive in a wide variety of other inflammatory diseases as well as acute rheumatic fever.[2] These tests are of no differential diagnostic value, but in patients with an established diagnosis of rheumatic fever, they roughly parallel and are useful indicators of the presence or absence of disease activity. As such, they are indispensable guides for following the clinical course of the disease.

The laboratory tests in the second group do not reflect disease activity. In supplying information relative to streptococcal infection, they indicate whether the stage has been set for the development of rheumatic fever. These aids include a *throat culture for the presence of group A beta-hemolytic streptococci* and the various *streptococcal antibody tests* (e.g., the ASO or antistreptolysin-O titer). These tests are nonspecific in the sense that they do not differentiate in any clinically useful or consistent way between those patients who do and those patients who do not develop rheumatic fever following streptococcal infections.[3] Nevertheless, when used with the clinical findings, these bacteriologic and immunologic tests help in determining whether the disease process is properly classified as acute rheumatic fever.

In patients with acute rheumatic fever streptococcal antibody tests are in general a more reliable indicator of recent streptococcal infection than throat cultures. At the time rheumatic fever is suspected, a routine throat culture is of rather limited value. By this time, the group A beta-hemolytic streptococci may have been eradicated by antibiotic therapy or, even without antibiotics, may be so reduced in number as to evade detection in a single routine culture. Therefore, a negative culture is of no significance. Repeated throat cultures and cultures by special technics result in the demonstration of the infecting organism in a higher percentage of patients.[4]

The great variety of antigenic products of group A streptococci provides a rather wide selection of antibodies that can be used as

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This work was done during the tenure of a Career Investigatorship of the American Heart Association (Dr. Wannamaker), was conducted, in part, under the sponsorship of the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of the Surgeons General, Department of the Army, Washington, D.C., by a research grant (H-1829 C2) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service, and by the Minnesota Heart Association.

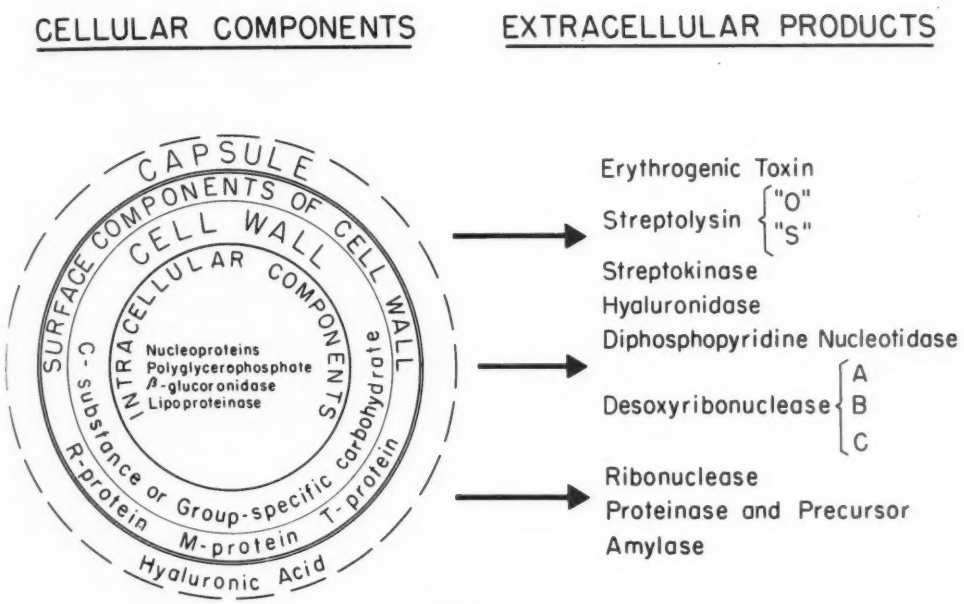

Figure 1

Diagrammatic representation of known cellular components and extracellular products of group A streptococci.

indicators of recent streptococcal infection. Those which have been studied most thoroughly following natural streptococcal infection in man include antibody responses to streptolysin O, erythrogenic toxin, type-specific M protein, streptokinase, hyaluronidase, the desoxyribonucleases, and diphosphopyridine nucleotidase. With the exception of M protein, which is a surface component of the cell, these substances are extracellular products of the streptococcus, i.e., products released into the surrounding medium (fig. 1). In addition to their antigenicity they are all biologically active. Indeed, it is largely by their biologic activity that they are known, since chemically pure preparations have not been obtained. Furthermore, specific antibody for each product is determined by neutralization of its specific biologic activity. In studying human infections antibodies to streptococcal substances other than those named have not proved satisfactory either because they are nonantigenic (streptolysin S, hyaluronic acid), poorly antigenic (proteinase, group-specific carbohydrate), nonspecific for beta-hemolytic streptococci (nucleoprotein fraction), or poorly differentiated in unabsorbed sera (T protein, R protein, group-specific carbohydrate). Naturally occurring antibodies to other substances (ribonuclease, amylase, beta glucuronidase, lipoproteinase, and polyglycerophosphate) have not been extensively studied in human beings.[5] Antibody to polyglycerophosphate is not likely to be useful in studying streptococcal infections in man because the antigen is present in a number of other gram-positive bacteria.[6]

Earliest interest in streptococcal immunology quite naturally focused on those antibodies that neutralize streptococcal substances associated with the most striking clinical and laboratory manifestations of infection. Attention was drawn to antibody neutralizing the erythrogenic toxin of scarlet fever (antitoxin), to antibodies responsible for protection in experimental infections (antibodies to the M proteins), and to antibodies inhibiting hemolytic substances produced by streptococci (streptolysins).

Antibodies to M Proteins (Type-Specific, Bactericidal, or Bacteriostatic Antibodies)

For some years immunity to streptococcal infections was in a state of confusion, confounded by a lack of knowledge of the antigenic composition of these organisms and by a preoccupation of many clinical investigators with scarlet fever and its antitoxin, which was subsequently shown to control the rash of scarlet fever but to afford no protection against invasion by streptococci.

The fundamental studies of Griffith[7] and of Lancefield[8] pointed to the antigenic diversity of these organisms and afforded a firm basis for their serologic classification. Griffith classified hemolytic streptococci into a number of types according to their T proteins (identified by agglutination reactions). A more natural classification arose from the studies of Lancefield. In the first place, she showed that hemolytic streptococci were divided into groups A through O according to the serologic specificity of the carbohydrate component of the cell wall (referred to as group-specific carbohydrate or "C" substance). Most infections in man, and all those resulting in acute rheumatic fever, are caused by group A hemolytic streptococci,[8] which have in their cell walls a common group-specific substance, known as group A carbohydrate. Lancefield has also shown that group A streptococci can be further subdivided, according to their specific M-proteins, into more than 40 different serologic types, which are designated numerically. Like T proteins, the M proteins are surface components of the streptococcal cell but their greater importance stems from their implication in the virulence of the organism and from the demonstration that immunity to streptococcal infection in animals and in man is dependent upon antibody to the specific M protein.[8, 9] Immunity is type-specific. Antibody to the M protein of one type does not protect against infection with a streptococcus producing M protein of a different type. This explains why multiple streptococcal infections occur.

Antibody to the M protein of the infecting strain (type-specific antibody) develops regularly following untreated streptococcal infections. It is relatively slow in appearing, sometimes requiring several months before it can be detected.[10, 11] This antibody is sharply suppressed by the administration of antibiotics, particularly penicillin.[11, 12] It often persists for many years, furnishing rather permanent protection against reinfection with strains of this specific type.[13]

Antibodies to the specific M proteins can be demonstrated by passive protection tests in experimentally infected animals. A more convenient test for type-specific or M antibody is the bactericidal or bacteriostatic test.[14] In this test, the M antibody is detected by its ability to facilitate the phagocytosis of streptococci of this type. Human blood lacking M antibody for the type being tested is used as a source of leukocytes. To this are added known quantities of streptococci, producing M protein of the type being tested, plus known quantities of the serum being tested for M antibody. After a suitable period of incubation and rotation to facilitate surface phagocytosis, the number of surviving chains of streptococci is estimated by counting the colonies produced by an aliquot seeded into a blood agar plate.[13] The reduction in colony count as compared with suitable controls indicates in a roughly quantitative fashion the amount of type-specific antibody present. This is a complex biologic test system, subject to a number of variables. More recently it has been shown that type-specific antibody can also be identified by its ability to promote the formation of long chains by streptococci of homologous type growing in broth culture.[15] This test is simpler to perform than the other 2 but is probably less quanitative and requires special strain variants, which will readily form long chains in the presence of type-specific antibody.

Because of their type-specific nature and of their persistence for long periods of time, antibodies to the M proteins are of no value as a general indicator of the probability of recent streptococcal infection. Moreover, the complexity of the tests involved and the multiplicity of different M antigens generally restrict their usage to special research studies

The demonstration, however, that infection by certain specific types of streptococci is associated with the development of acute nephritis[4] has stimulated new and widespread interest in these antibodies as a source of information regarding the infecting type in patients from whom the organism can no longer be isolated.

Antitoxin (Antibody to Erythrogenic Toxin)

Antitoxin titers have proved to be rather unsatisfactory measurements of streptococcal antibody not only because of the existence of more than one erythrogenic toxin,[16] but more seriously because erythrogenic toxins and their antitoxins can only be measured in terms of a skin reaction in susceptible human subjects or animals. This results in gross limitations in precise standardization and accurate quantitation of antibody levels.

Antistreptolysin O

Within the past several decades, antibody to streptolysin O (antistreptolysin O, sometimes designated simply as antistreptolysin or commonly abbreviated ASO or ASL) has replaced antibody to erythrogenic toxin as the classic antibody for studying the response to streptococcal infections in man. This antibody is easily quantitated and standardized, and has been extensively studied and widely used. Since antistreptolysin O is typical of the general pattern of antibody response following streptococcal infection, it will be considered in some detail.

Confusion concerning the hemolytic properties of streptococci was clarified by the work of Todd,[17] who demonstrated that streptococci produce 2 kinds of hemolysin, streptolysin S and streptolysin O. Streptolysin S is oxygen-stable and is responsible for the clear (beta) hemolysis surrounding colonies of *Streptococcus pyogenes* grown on the surface of aerobically incubated blood agar plates. The letter S refers to the fact that serum greatly enhances the formation of this hemolysin. Streptolysin S is inhibited by labile lipoprotein complexes in normal human serum, but neutralizing antibody for streptolysin S does not develop following natural infection in man nor following injection of this antigen into laboratory animals. In contrast, streptolysin O is antigenic upon injection and antibodies are readily demonstrated in the sera of patients following streptococcal infections. Streptolysin O is so named because it is oxygen-labile, existing in 2 forms: the inactive (oxygenated) form which can be reversibly reactivated to the active (reduced) form. Both streptolysin O and S may contribute to the hemolysis of subsurface colonies of *Streptococcus pyogenes*. Streptolysin O is inhibited by specific antibody and by cholesterol and certain other lipids.[18]

Streptolysin O may be stored in its active (reduced) state or may be reactivated just prior to use by the addition of a reducing agent (e.g., cysteine). The activity of streptolysin O is measured by its ability to hemolyze red cells. In tests for antistreptolysin O, varying dilutions of serum are incubated with constant standard amounts of active hemolysin. These mixtures are tested for residual (unneutralized) hemolytic activity by incubation with a standard amount of rabbit red cells. The antistreptolysin-O titer is that dilution of serum which will completely neutralize hemolytic activity under these standard conditions.

A rise in antistreptolysin-O titer can be interpreted as reliable evidence of a streptococcal infection. Because hemolytic streptococci of groups C and G also produce streptolysin O, an increase in antistreptolysin-O titer may follow infection with these groups as well as with group A streptococci. Other species of bacteria, such as the pneumococci and the clostridia, produce hemolysins that are immunologically related to those of group A streptococci, but the degree of cross reactivity does not appear to be sufficient to result in practical difficulties. Immunization procedures and infectious diseases of nonstreptococcal etiology do not result in an increase in antistreptolysin-O titer.[3] Although cholesterol is known to be a potent inhibitor of streptolysin O, the cholesterol of normal serum does not inhibit streptolysin O, as it is apparently in a state in which it does not combine with strep-

tolysin O.[18] On the other hand, the presence of nonspecific lipoprotein inhibitors in the sera of patients with hepatitis and in sera that have become contaminated may result in spuriously high titers that do not reflect true antibody inhibition.[18] Technical difficulties, other than contaminated sera, which may lead to false titers include the use of streptolysin-O preparations which are incompletely activated. Commercial preparations of streptolysin O should be used as soon as reconstituted. On standing, a portion or all of the preparation may convert to a nonhemolytic state in which it will nevertheless still combine with antibody. Even when freshly prepared hemolysin is used, it is hazardous to assume that the potency of the preparation has not changed since standardization by the manufacturer. One, or preferably several, standard antisera should be titrated as controls in each set of antistreptolysin O determinations.

In patients with well-documented streptococcal infections, a rise in antistreptolysin-O titer can often be demonstrated after 1 week, but titers do not reach maximal levels until 3 to 5 weeks after infection.[19] There is considerable variation in the rapidity with which titers return to preinfection levels. The cause for this individual variation is largely unknown although a number of factors may affect the rate of decline. For example, steroid therapy accelerates the rate of decline.[20] Other factors, which may influence the rate of fall in titer, include persistence of the organism, and perhaps indirectly the presence or absence of tonsils and the administration of antibiotics.[21] Reinfection may result in a sustained or continuously rising titer. Generally, in the absence of reinfection, titers tend to decline gradually and to approach preinfection levels by 6 to 12 months.[22]

The magnitude of the antibody response also shows considerable variation. Factors such as the nature or the severity of the preceding infection or the serologic type of the infecting group A streptococcus may influence the magnitude of the antistreptolysin-O response.[10, 23] Of considerable attraction is the observation that patients who develop rheumatic fever are in general more likely to show a higher antibody response than those whose infection is not followed by this late complication.[3, 10, 23] This suggests that rheumatic individuals are "immunological hyperresponders." An alternative interpretation is that individuals developing rheumatic fever have in some way been subjected to a greater antigenic challenge. More definitive information as to which interpretation is correct can be obtained by studying the antibody response of rheumatic subjects to injected antigens where the dose of antigen administered can be easily quantitated and controlled. Studies of the antibody response of rheumatic children to intramuscular injection of a concentrate containing streptolysin O suggest that, as a group, these children show greater antistreptolysin-O responses than nonrheumatic children.[24] Interpretation of this study, however, is complicated by the varying doses injected and by the different average initial titers in the rheumatic and nonrheumatic groups. If rheumatic individuals are "hyper-responders," it appears that this immunologic hyperresponsiveness is specific for streptococcal antigens. Most studies have indicated no unusual antibody response in rheumatic subjects following the injection of nonstreptococcal antigens.[4, 25] Moreover, the difference in response to streptococcal antigens is by no means constant. Of the 20 rheumatic children injected with streptolysin O, 5 showed no detectable antibody response.[24] Also the difference in antibody response following natural infection between those who do and do not develop rheumatic fever[3] is based on an average figure, and there is a wide area of overlap of individual responses in the 2 groups of patients. Indeed, some patients who develop rheumatic fever show no detectable rise in antistreptolysin-O titer.

Occasional differences in the antibody response may be related to differences in the production of streptolysin O by strains of group A streptococci.[26] Although it is possible to quantitate production under in vitro conditions, it is not possible by present techniques to estimate in vivo production. Experience

ith injected antigens, however, where the mount of antigen can be precisely controlled, as indicated considerable individual variation in antibody response due to unknown host ctors.[24, 27]

Two factors that appear to influence both he magnitude and the frequency of the antistreptolysin-O response are previous exposure to the streptococcal antigen and, perhaps indirectly, the age of the patient. It is well known from experimental studies with a variety of antigens that antibody responses are less impressive in patients or animals who are experiencing their first exposure to an antigen (primary response) than in those who have been previously exposed (secondary response).[27] Streptococcal infections are not only fairly common but repeated infection occurs with reexposure to antigens encountered previously. In most clinical situations, we are not dealing with the patient's first experience with streptococcal antigens. Therefore, the frequency and the degree of antibody response will depend upon previous experience with the streptococcus. Such factors as the number of past streptococcal infections, the length of time since the last infection, and the height of the residual antibody level at the time of reinfection may be involved.

It is generally agreed that antistreptolysin-O responses are usually poorer in infants than in older children or adults.[28] Except in the first few months of life, it would seem unlikely that poor responses can be attributed to an immaturity of immunologic mechanisms. It seems more likely that responses tend to be poorer because this is the infant's or child's first encounter with streptococcal antigens (primary response).[29]

The natural course of streptolysin-O response can be modified by the administration of drugs. Cortisone may delay antibody development.[30] Penicillin may modify the antistreptolysin-O response even more strikingly, by reducing the over-all number of responders and by influencing the magnitude of the antibody response.[31, 32] The effect of penicillin is related to the time therapy is started, to the dosage employed, and to the length of time given. Bactericidal drugs such as penicillin are more likely to influence the antibody response than bacteriostatic drugs such as sulfonamides and tetracyclines.

Table 1

Dilution Schemes Commonly Used in Streptococcal Antibody Titrations

Logs	Antibody Titers in Various Dilution Schemes				
	2-fold	1½-fold (KAPLAN)	1¼-fold or 0.1 Log (C.A.R.D.)	(HODGE & SWIFT)	(RANTZ)
1.0	10				12
1.2					
1.4	20	25		25	
1.6	40	36			
1.8		56	50 63	50	50
2.0	80	83	83 100	100	100
2.2	160	125 179	125 159 200	150	125 166
2.4	320	278	250 317	250 300 350	250 333
2.6		417	400 500	400 450 500	500
2.8	640	625	625 833	600 700 800	625 833
3.0		900	1000	900 1000	
3.2	1280	1400	1250 1585	1250 1400 1600	1250
3.4	2560	2100	2000	1800 2000	2500

Aside from biologic factors and the influence of drugs, certain differences in reports of the frequency and magnitude of antistreptolysin-O responses are inherent in the schemes of dilution increments used in measuring antibody. In table 1 are listed a variety of dilution schemes that have been used for measuring antistreptolysin O or other streptococcal antibodies. Most of these are devised according to a plan that makes it technically easy to make dilutions in a serial fashion. Some are constructed in a logical mathematical pattern, showing increments that are logarithmic. These result in a straight-line progression, as shown in figure 2. The slopes of the 3 lines representing these dilution methods vary considerably. The 2-fold system progresses to relatively high titers within a few dilutions,

whereas the 1½-fold (Kaplan) method[33] progresses more slowly and the 1¼-fold or 0.1 log (CARD)[21] system shows even smaller increments. The design of the 2 other schemes results in titers that follow no constant mathematical sequence. The method of Hodge and Swift[34] is by arithmetical progression, which changes at intervals. This method produces an irregular curve, but has the advantage of resulting in numerical titers that are easy to remember. Although logarithmic in trend, the method of Rantz and Randall[35] is irregular in progression and results in titers that are more difficult to remember. Despite these disadvantages, this latter method is becoming more and more widely used because it is often the scheme which accompanies the commercially available reagents.

Obviously, the spacing of increments in the particular scheme being used will influence to some extent both the percentage of patients showing an "antibody response" and the "magnitude" of these responses. For example, within the limits of reproducibility, an antibody rise will be more frequently demonstrated by schemes with smaller increments. Moreover, within any given scheme, the percentage of patients exhibiting an antibody rise will vary, depending upon the level of the initial antibody titer. Although some of the schemes are irregular, in general the arithmetic increments become progressively larger as one moves from the lower to the higher dilutions. Consequently, an antibody response is more likely to be demonstrated in patients with low initial titers than in patients with high initial titers. To illustrate, with the 0.1-log increment system (CARD), a 100-unit rise in a patient whose initial titer is 63 units will result in a 4-tube increase, whereas an identical rise in a patient whose initial titer is 500 would not be detected (table 1).

With careful technics, increments as close as 0.1 log can be accurately and reproducibly measured, and increases of 0.2 log (2 tubes) can be accepted as evidence of a rise in titer. Following well-documented untreated streptococcal infections, antistreptolysin-O responses can be demonstrated in about 80 to 85 per cent of patients.[21, 23] In some series the percentage is lower (60 to 80 per cent).[3, 36–39] This may be due to a number of factors, including antibiotic therapy, age of the patient, high-initial antibody titers, infection with strains that are poor streptolysin-O producers, and dilution of the series with patients who by clinical or bacteriologic criteria appear to be infected with streptococci but whose current illness is indeed due to some other agent.

In the usual clinical situation, an antistreptolysin-O titer is not obtained until rheumatic fever or some other complication of streptococcal infection is suspected. By this time the antibody titer may be at or near its peak and it may be impossible to demonstrate an antibody rise. Without a baseline titer for comparison, it is considerably more difficult to interpret the meaning of a titer taken at the time rheumatic fever is suspected. One must resort to a comparison of this single antibody determination with an average level in the population. Some titers that are low in comparison with the average population may represent a definite increase over the baseline titer for this individual and may, therefore, represent true streptococcal infection. Other titers may be high but may represent a residual from a streptococcal infection too distant to be directly related to the onset of rheumatic fever. The difficulty is compounded by the fact that average antistreptolysin-O levels may vary for different populations by age, economic status, geographic area, season, year, and other factors related to the frequency of streptococcal infections.[28]

Because of the ubiquity of streptococcal infections and of the commonness of streptolysin O as an antigen of group A streptococci, sera from normal individuals generally show some antibody to streptolysin O, reflecting contact with the streptococcus at some time in the distant past. These low titers (< 250 Todd units) are commonly found in school-age children and young adults who have not had a recent streptococcal infection.[28] The antibody is passively transferred to the fetus via the placental circulation, so that levels in cord bloods and in newborns are equal to or slightly

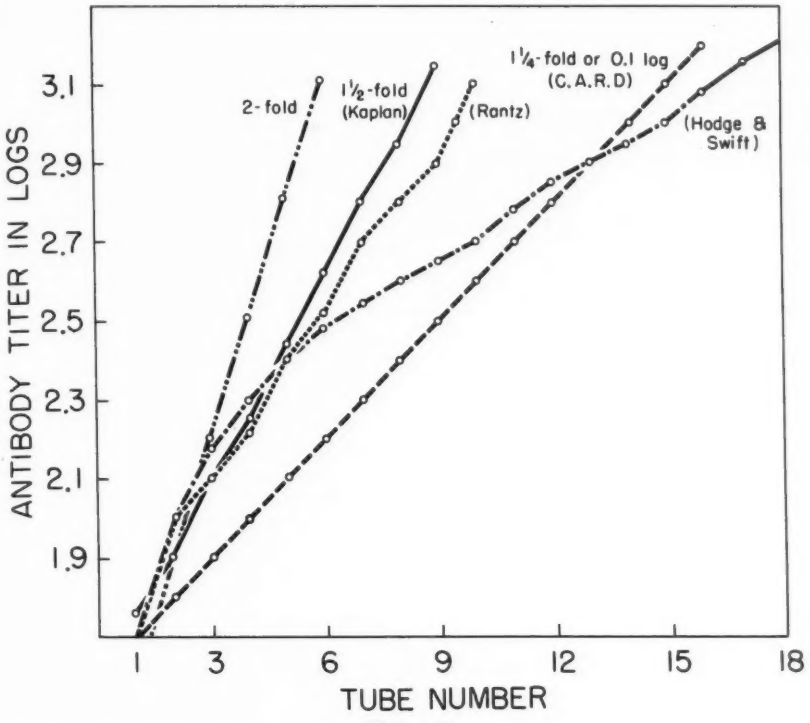

Figure 2

Graphic comparison of dilution schemes commonly used in streptococcal antibody titrations. (For purposes of comparison, the titer in each system closest to 50 units has been designated as tube no. 1.)

in excess of those of the mother.[40] This passively acquired antibody is lost during the first half year. Consequently, between 6 months and 2 years of age antistreptolysin-O titers are usually very low or not detectable. After infancy and particularly when the child reaches school age, the chances of acquiring a streptococcal infection increase, so that average antistreptolysin levels tend to increase during this period. Highest normal levels are found in the school-age child. These tend to stabilize or decline slightly in the young adult and to decrease in later years as the frequency of streptococcal infection decreases.

In normal school-age populations about 80 per cent of individuals will have a titer of 333 units or less (table 2). In young adults a titer of greater than 200 Todd units may be out of line with the general population. In older adults, except those in situations where exposure to streptococcal infection is high, titers greater than 100 to 150 units may be considered uncommon.[28] Adults who may be unusually exposed to streptococcal infection include those in the military services and mothers of school-age children.

In spite of the relative paucity of data on antistreptolysin-O titers in "normal" populations and in spite of some degree of overlapping of titers in "normal" and "rheumatic" populations (table 2), the occurrence of an isolated, single titer that is quite high (500 units or more) is reasonable evidence of a recent streptococcal infection. Furthermore, the infection is probably recent enough to be causally related to the present illness suspected of being acute rheumatic fever. In about 80 per cent of patients with acute rheu-

matic fever, the antistreptolysin-O titer during the first 2 months of illness is 250 units or higher.[22] If the admission titer is low or borderline, further specimens taken at weekly intervals sometimes reveal an elevated titer, since the level of antibody may continue to rise for some time after the onset of acute rheumatic fever. In patients with subsiding, inactive, or chronic rheumatic fever the antibody titer has frequently declined to normal levels.[22] Because of the prolonged latent period of several to many months frequently observed between the streptococcal infection and the onset of acute chorea, patients presenting with this rheumatic manifestation often show antistreptolysin titers that have returned to normal levels.[47]

The determination of antistreptolysin O is probably the best routine streptococcal antibody test available, although the extent of overlapping of values between normal and acute rheumatic fever populations does not make it an ideal differential test. Since it was one of the first such tests studied, it has been widely used in investigative work and, with the commercial availability of the necessary reagents, has become a routine test in many hospital laboratories. The units of antibody measured are fairly well standardized in terms of the Todd unit of the original procedure. Therefore, in the various modifications of this method currently in use, one can be reasonably sure, with careful attention to technic and standardization, that the antibody titers obtained in one laboratory are comparable to those obtained in others. Moreover, the percentage of patients with streptococcal infection who subsequently show an antibody response is as high as or higher than that with any other single streptococcal antigen. Nevertheless, about 20 per cent of patients fail to show an antibody response to streptolysin O, and a similar percentage of patients with acute rheumatic fever present with low or borderline antistreptolysin-O titers (250 units or less).[3, 23] Consequently, a diagnosis of acute rheumatic fever can never be excluded on the basis of the antistreptolysin-O titer alone.

The failure of certain patients with streptococcal infection to show an antistreptolysin O response and the consequent finding of low or borderline titers in some patients with acute rheumatic fever has stimulated interest in other streptococcal antibodies that may be used as secondary tests. Determination of antibody to one or more additional streptococcal antigens is of value because titers of antibody to one streptococcal antigen sometimes do not parallel those of another. For example, a patient may have a high antistreptolysin-O titer and a low antihyaluronidase titer or vice versa. Therefore, if a secondary test is performed, the percentage of patients showing an elevated titer is increased and if multiple antibody tests are done, this will approach 100 per cent.[3, 22] A number of secondary tests are available: antistreptokinase, antihyaluronidase, antidiphosphopydrine-nucleotidase (anti-DPNase), and antidesoxyribonuclease B (anti-DNAse B).

Antistreptokinase ("Antifibrinolysin")

The phenomenon of liquefaction of human fibrin clots by broth cultures or culture filtrates of beta-hemolytic streptococci as reported by Tillett and Garner in 1933,[48] was ascribed first to "fibrinolysin." Further studies indicated that this streptococcal substance does not lyse fibrin directly but results in the conversion of a normal serum component (plasminogen) to an active proteolytic enzyme (plasmin). Plasmin digests not only fibrin but also other protein substrates. Thus, the term fibrinolysin is a misnomer in several respects, and it has been generally replaced by streptokinase when referring to the streptococcal substance that activates the plasminogen-plasmin system. This system is a complicated one, involving not only the factors already named but also inhibitors and other activators.

With the establishment of the antigenicity of streptokinase in man,[49] it became apparent that the estimation of the corresponding antibody levels in human sera might serve as an indication of streptococcal infection. A quantitative method for assaying the antistreptokinase levels of human sera was introduced by

Table 2

Usual Limits of Streptococcal Antibody Titers in Normal Individuals and in Patients with Early Acute Rheumatic Fever

Antibody	Upper limits in normal population*				Lower limits in early acute rheumatic fever†	
	5 - 12 years‡	*References*	Young adults‡	*References*	Children & adults‡	*References*
Antistreptolysin O	**333**	*28*	**200** (166-250)	*28, 39, 41, 42*	**250** (166-400)	*41 - 46*
Antistreptokinase			**115** (8 -150)	*39, 41*	**200** (160-250)	*22, 46, 50*
Antihyaluronidase	**110** (100-128)	*42, 59*	**80** (60-100)	*42, 59*	**300** (256-500)	*42, 44, 45, 59*
Anti - DPNase			**130**§	*70*	**175**	*70*
Anti - DNAse B			**80**§	*70*	**320**	*70*

*Approximately 80 per cent at this level or lower.

†Approximately 80 per cent at this level or higher.

‡Where several different values were obtained from the references cited, the range is indicated in parenthesis and an approximate median value is represented by the figure in bold face.

§Includes some children as well as young adults.

Kaplan in 1946.[33] This method involved a neutralization test in which a constant, standardized amount of streptokinase was incubated with serial dilutions of the serum to be tested, following which an indicator system consisting of fibrinogen, plasminogen, and thrombin was added. The end-point of the test was defined as the reciprocal of the highest dilution of serum that completely prevented lysis of the clot during a second period of incubation.

Information on antistreptokinase levels is much less extensive than that for antistreptolysin O, particularly in normal populations (table 2). The rise in antistreptokinase titer following a streptococcal infection with and without complications follows the same general pattern as the antistreptolysin-O titer, although several studies indicate that antibody responses occur less frequently to streptokinase.[21, 37, 39] The relative infrequency of response to streptokinase may be explained by marked differences in production of this substance by infecting strains.[51] Another possible explanation would be the production of several immunologically distinct streptokinases by different strains of streptococci, but the evidence on this point is at present conflicting.[52, 53]

Apart from the relative infrequency of antibody response reported in these studies, antistreptokinase determinations have not been altogether satisfactory because of difficulties in standardization. The various components of the test system are not available in a pure state. Reproducible results can be obtained in one laboratory with the use of a single lot of substrate and of other components, but these results may not compare with those of other laboratories. Moreover, the sera being tested may contribute varying amounts of nonantibody substances (e.g., nonspecific inhibitors, plasminogen) that may affect the test system. Attempts to overcome these difficulties have been made by modifying the antisera in various ways prior to testing. For example, heating will inactivate the plasminogen in antisera but the test results may still be influenced by the fact that heat-inactivated plasminogen binds streptokinase.[54] Another method consists of separating antibody globulin from the antisera prior to testing.[54] This appears to offer a more promising and reliable approach to the measurement of antistreptokinase but makes the routine determination of this antibody somewhat complicated. As a consequence of the above considerations, the

antistreptokinase test has been generally less acceptable and less widely used than other streptococcal antibody tests.

Antihyaluronidase

Because of possible implications in the pathogenesis of rheumatic fever, a considerable flurry of interest followed the demonstration that group A streptococci produce an enzyme that depolymerizes hyaluronic acid, a constituent of synovial fluid and other connective tissues.[55] This streptococcal enzyme is adaptively produced, i.e., production is stimulated by the addition of substrate to the culture medium.[56] Only group A streptococci of types 4 and 22 produce appreciable amounts of the enzyme under in vitro conditions.[57] The hyaluronidase of group A streptococci is immunologically distinct from the hyaluronidases from other sources (other groups of streptococci, other bacteria, mammalian tissues).[58, 59]

This enzyme is inhibited by 2 factors present in human sera. The first, a nonspecific inhibitor (NSI) inhibits hyaluronidase-activity, regardless of the source of enzyme.[60] It is heat-labile and requires magnesium ions for its action. This nonspecific inhibitor is an acute-phase reactant rather than an antibody; as such it develops early in infection, subsiding during convalescence unless suppurative or nonsuppurative complications develop.[2] The specific inhibitor (SI) is a true antibody, which develops several weeks after the onset of streptococcal infection, persists after the subsidence of inflammation, appears in the gamma-globulin fraction of serum, and neutralizes the hyaluronidase of group A streptococci specifically. It is heat-stable and does not require magnesium ions for its activation.[2, 61]

The in vitro determination of antihyaluronidase in human sera is based on the specific inhibition of the capacity of streptococcal hyaluronidase to digest hyaluronic acid. Nonspecific inhibitor is inactivated by heating the sera at 56°C. for 30 minutes. Two commonly used methods in the determination of hyaluronidase activity are the turbidimetric and mucin clot prevention (MCP) methods.[62] Both methods depend upon a property of hyaluronic acid that results in binding with protein in an acid medium. Under the conditions of the first test the hyaluronic acid-protein complex appears as a turbid suspension, whereas in the second test the complex forms a gelatinous mucin clot. Both tests may be adapted for the estimation of antibody. Though the turbidimetric method is more quantitative, the MCP test is the more widely used because of its adaptability in the assay of large numbers of sera. A modification of the latter test has been reported by DiCaprio et al.[63] A reliable substrate for this test is somewhat difficult to prepare, and commercial preparations are not always sufficiently highly polymerized to be suitable.

Standardization of antihyaluronidase titers has proved difficult, and the titers obtained in various laboratories vary quite markedly (table 2). This is apparently due to a number of factors including the variability encountered in lots of substrate, minor variations in the test procedure (which is greatly susceptible to critical factors such as salt concentration and pH),[62] and difficulty in reading the end points. Because of this latter difficulty one cannot use serum increments as close as those that may be used with antistreptolysin O. Dilutions at closer intervals than 2-fold have usually proved unsatisfactory, and some investigators have used 4- or 5-fold dilutions.

The general pattern of antibody response to hyaluronidase is similar to that of streptolysin O, although considerable variation is noted in the levels reported by various authors for normal subjects and for patients with acute rheumatic fever (table 2). Several investigators have been impressed with the higher titers found in patients with acute rheumatic fever when compared with convalescent uncomplicated streptococcal infections, suggesting that the differential rise with this antibody might be greater than that with other antibodies such as antistreptolysin O.[43, 44, 64] The percentage of patients developing an antihyaluronidase response following

streptococcal infection is somewhat lower than the percentage developing an antistreptolysin-O response.[37, 45, 63] This may be due in part to the technical difficulties in reliably demonstrating small increments of antihyaluronidase. It is indeed rather curious that so many patients do show an increase in antihyaluronidase titer following streptococcal infection, since only a few strains (types 4 and 22) produce appreciable amounts of this enzyme in vitro. Possible explanations for this discrepancy are that in vivo environments may be more favorable for production of this enzyme[65] or that it may be present as a proenzyme.

The wide differences in titers between normal individuals and patients with rheumatic fever (table 2) suggest that this might be one of the better differential serologic tests in acute rheumatic fever; but because of difficulties in standardization, extreme differences in titers reported in the literature, and certain technical difficulties, the antihyaluronidase determination has not been altogether satisfactory as an antibody test. Nevertheless, until recently this has probably been the best available and most widely used streptococcal antibody test other than the antistreptolysin-O determination. Two new antibody tests, anti-DPNase and anti-DNAse B have recently been described that appear to have certain advantages as secondary antibody tests.

Anti-Diphosphopyridine-Nucleotidase (Anti-DPNase, ASDA)

The identification and characterization of an enzyme in group A streptococcal culture supernates that splits DPN (coenzyme I, cozymase, diphosphopyridine nucleotide) was reported by Carlson et al. in 1957.[66] There appears to be considerable strain variation in the in vitro production of streptococcal diphosphopyridine-nucleotidase (DPNase), with type 12 and other nephritogenic strains being among the better producers. Kellner et al.[67] have presented evidence that this enzyme is antigenic in animals and in man. They referred to the antibodies directed against streptococcal DPNase as ASDA ("antistreptococcal diphosphopyridine-nucleotidase activity") although antistreptococcal DPNase or anti-DPNase are perhaps preferable abbreviations, which are less likely to be confused with antibody to the streptococcal desoxyribonucleases (streptodornases).

The assay of antibody to streptococcal DPNase is based on the ability of sera containing such antibody to neutralize the specific action of the streptococcal enzyme in splitting a standard DPN substrate. At the end of the reaction period, the enzyme activity is stopped by the addition of sodium cyanide and the undigested DPN is measured spectrophotometrically as a cyanide-substrate complex. A unit of DPNase activity has been arbitrarily defined as that amount which will destroy 0.01 micromoles of DPN under the conditions of the test. One unit of anti-DPNase is that amount of antibody which will neutralize 100 units of the enzyme. Kellner et al.,[67] using the spectrophotometric assay procedure for DPNase described by Colowick et al.,[68] reported reproducibility with a range of plus or minus 30 per cent. Bernhard and Stollerman, with a minor modification of the above methods, obtained results showing a standard deviation that was within 10 per cent of the mean titer in replicate determinations made on a pool of human sera.[37]

The initial survey made on random sera by Kellner et al.[67] showed a pattern of antibody titers similar to that for other streptococcal antibodies. The lowest titers were present in children between 6 months and 5 years, while infants up to the age of 6 months showed a mean titer similar to the adult. A definite rise in titer was observed in approximately 75 per cent of patients following streptococcal infection. These findings were confirmed by Bernhard and Stollerman,[37] who reported a significant rise of the anti-DPNase titer in 63 per cent of children with pharyngitis associated with positive culture for group A streptococci as compared with a rise of antistreptolysin-O titer in 62 per cent of patients in this group. In patients with acute rheumatic fever, 87 per cent showed an elevated anti-DPNase titer, whereas an equal percentage showed an elevated antistreptolysin-O titer.

Although many strains of group A strepto-

cocci fail to produce DPNase in vitro,[69] it appears that the majority of patients show an antibody response to this enzyme following streptococcal infection.[37, 70] This paradoxical situation is similar to that previously noted in the case of antibody responses to hyaluronidase. Only a few studies[37, 67, 70] have been made of levels of this antibody in normal and rheumatic populations, and some of these are not interpretable in terms of the categories in table 2. Therefore, the figures given must be considered preliminary.

Anti-DPNase is relatively easy to determine, although it requires the use of a spectrophotometer or a photocolorimeter. A 95 per cent pure substrate can be purchased inexpensively. Since the test is based on a quantitative chemical determination of the undigested substrate, it is quite accurate and reproducible. Thus, the anti-DPNase test appears to be one of the most promising of the new antibody tests available.

Antidesoxyribonuclease B (Anti-DNAse B)

The depolymerization of desoxyribonucleic acid (DNA) by culture supernates of group A streptococci has been independently reported by Tillet et al.[71] and by McCarty.[72] This activity was ascribed to an enzyme called streptococcal desoxyribonuclease (DNAse) or streptodornase. In vitro studies have indicated that virtually all group A strains show DNAse activity in relatively large amounts. It was, therefore, somewhat disappointing when it was originally found that comparatively few patients appeared to develop antibody following natural infection.[73]

This paradox (of a reverse sort from that observed in the antibody response to hyaluronidase and to DPNase) was resolved when it was shown that group A streptococci can produce 3 distinct desoxyribonucleases, DNAses A, B, and C.[74] The 3 enzymes have been differentiated in a number of ways, but one of the most important differences is their serologic specificity. Antibody against one of the enzymes neutralizes the activity of that enzyme but not that of the other 2.

Since most strains of group A streptococci produce predominantly DNAse B, it is not surprising that low titers of antibody to this enzyme are often found in normal individuals and that an antibody rise occurs regularly following streptococcal infection. The frequency of the anti-DNAse B response compares favorably with that for antistreptolysin O. High titers are also frequent among patients with acute rheumatic fever (table 2).[38] The titer limits in normal individuals and in patients with acute rheumatic fever, as given in table 2, must be considered tentative until additional and more extensive studies are available.

Anti-DNAse B is measured by its ability to neutralize the specific DNAse-B activity in a test that superficially resembles the mucin clot prevention (MCP) test.[38, 73] Serum is heated to destroy circulating mammalian DNAse activity, and dilutions are incubated with a constant amount of DNAse B. The mixture is then tested for unneutralized enzyme activity by adding a standard amount of substrate (DNA). After further incubation, alcohol is added and undigested substrate forms a white clump. With care in standardization, the test can be read at serum dilutions similar to those employed in the antistreptolysin test (0.1 log or greater), although 2-fold dilutions are more satisfactory for general use. Suitable group A strains can be found that produce DNAse B in great excess of the other 2 enzymes, so that the crude culture supernate can be used as a source of enzyme. The substrate can be prepared without too much difficulty or may be obtained commercially. Not all commercial preparations are satisfactory as a highly polymerized preparation is essential.

The wide distribution of DNAse B among strains of group A streptococci and the frequency of antibody response following streptococcal infection establish this as an antibody test that compares favorably with that for streptolysin O. In patients with rheumatic fever who present with low or borderline antistreptolysin-O tests, this antibody is frequently unquestionably elevated.[38] These findings recommend it as one of the best available secondary tests.

Conclusions

Laboratory tests specifically indicating the presence of acute rheumatic fever are not presently available. Although antibody tests do not differentiate the patient with acute rheumatic fever from the patient who has recently recovered from a streptococcal infection without such a complication, they are useful as indicators of the probability of a recent streptococcal infection which could have triggered the development of acute rheumatic fever.

The antibody response to different streptococcal antigens varies independently following infection. No more than about 80 to 85 per cent of patients show a response to any single antigen, but if antibody responses to multiple antigens are looked for, this approaches 100 per cent.

Because the antistreptolysin-O (ASO) determination has been widely used and well standardized, it is probably the best antibody test available. However, some patients fail to show an antibody response to streptolysin O following streptococcal infection, and the values for normal populations and patients with acute rheumatic fever show appreciable overlapping. Therefore, some patients with acute rheumatic fever will present with low or borderline ASO titers. In such patients, the performance of one or more secondary antibody tests is desirable.

In the past the antihyaluronidase (ASH) test was probably the best secondary test available. Recently 2 new antibody tests have been described that seem to have certain advantages over the antihyaluronidase test. The anti-diphosphopyridine-nucleotidase (anti-DPNase or ASDA) test appears to offer some advantage in standardization in that the undigested substrate can be determined chemically. Although in vitro studies indicate that production of this enzyme is restricted to certain strains (mostly of the nephritogenic types), preliminary studies suggest that antibody responses are more broadly distributed. The second antibody test, antidesoxyribonuclease B (anti-DNAse B) measures neutralizing antibody for an enzyme that appears to be widely distributed among group A streptococci. Antibody responses to this enzyme occur regularly following streptococcal infection, and even those patients with acute rheumatic fever who show low titers of ASO often show distinctly elevated titers of anti-DNAse B.

Although no problem arises in those patients suspected of acute rheumatic fever who show markedly elevated ASO titers, the use of one or more secondary antibody tests is particularly helpful in patients whose ASO titer does not conform with the clinical impression.

Summario in Interlingua

Tests laboratorial capace a indicar specificamente le presentia de acute febre rheumatic non es disponibile a iste tempore. Ben que tests de anticorpore non differentia le patiente con acute febre rheumatic ab le patiente recentemente restablite ab un infection streptococcal sin le complication de febre rheumatic, tal tests es utile como indicatores del probabilitate de un recente infection streptococcal e assi del presentia de un causa al minus potential pro le precipitation del disveloppamento de acute febre rheumatic.

Le responsa anticorporee a differente antigenos streptococcal varia sin interdependentia post le occurrentia de un infection. Non plus que 80 a 85 pro cento del patientes responde positivemente a un antigeno individual, sed si le responsas a multiple antigenos es investigate, le proportion del casos positive approcha 100 pro cento.

Viste que determinationes a antistreptolysina-O (ASO) ha essite usate extensemente de maniera que iste methodo es ben standardisate, illo es probabilemente le melior del tests anticorporee nunc disponibile. Tamen, certe patientes non exhibi un responsa anticorporee a streptolysina-O post infectiones streptococcal, e le valores obtenite in le population normal e in gruppos de patientes con acute febre rheumatic monstra appreciabile areas de coincidentia. Per consequente, certe patientes con acute febre rheumatic manifesta basse o questionabile titros de ASO. In tal casos, le effectuation de un o plure secundari tests de anticorpore es desirabile.

In le passato, le melior del disponibile tests secundari esseva probabilemente le test a antihyaluronidase (ASH). Recentemente 2 nove tests a anticorpore esseva describite que pare haber certe avantages in comparation con le test a antihyaluronidase. Le test a anti-diphosphopyridina-nucleotidase (anti-DPNase a ASDA) pare offerer certe avantages de standardisation in tanto que le nondigerite substrato pote esser determinate chimicamente. Ben que studios in vitro indica que le production de iste enzyma es restringite

a certe racias (predominantemente del typo nephritogene), studios preliminari suggere que responsas anticorporee es distribuite plus largemente. Le secunde test a anticorpore, antidisoxyribonuclease B (anti-DNase B) mesura le anticorpore neutralisatori pro un enzyma que pare esser extensemente distribuite inter streptococcos de gruppo A. Responsas anticorporee a iste enzyma occurre regularmente post infection streptococcal, e mesmo le patientes con acute febre rheumatic qui exhibi basse titros de ASO va frequentemente exhibir distinctemente elevate titros de anti-DNase B.

Ben que nulle problema existe in patientes suspecte de acute febre rheumatic quando illes exhibi marcatemente elevate titros de ASO, le uso de un o plure tests secundari a anticorpore es specialmente utile in patientes in qui le titro de ASO non congrue con le impression clinic.

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Standards for Centers Caring for Patients with Congenital Cardiac Defects

Report of the Committee on Congenital Heart Defects

THE purpose of this report is to provide standards for services and necessary equipment for centers responsible for the diagnosis and surgical care of patients with congenital defects of the heart and blood vessels. Skill in this field is dependent on training and on continuous extensive experience which in turn is related to the caseload of an institution. Before establishing such a center, careful consideration should be given to the real need in the city or area for this highly specialized type of diagnostic workup and surgical correction. Many skills and facilities needed are not ordinarily available outside a medical center.

Accurate diagnosis of the congenital cardiac malformation is a prerequisite to cardiac surgery. To have a diagnostic center for this purpose is, therefore, of prime importance for any hospital in which cardiac surgery is performed.

This type of work requires highly developed teamwork on the part of the pediatric or medical diagnostician, surgeon, anesthesiologist, roentgenologist and members of allied services. It is not advisable to have a sharp division between diagnostic and surgical responsibilities. The center in which cardiac surgery is done must be approved for resident training in surgery and in internal medicine or pediatrics. It must be ultimately responsible for both definitive diagnosis and surgical care. The essential requirements for a diagnostic center follow below.

I. Diagnostic Staff

A. Physicians

The following specialists should be on the team:

1. A *pediatric cardiologist* or a *cardiologist* who is thoroughly familiar with the diagnostic features and care of patients with congenital cardiac malformations is essential. The importance of a pediatrician on the team is evident when it is realized that more than one half of such patients are in the pediatric age group.

2. A qualified *radiologist* who has had additional training in the cardiovascular field.

3. A qualified *surgeon* with training in cardiovascular surgery who should be directly responsible for the surgical care of the patients.

4. A *physician-anesthesiologist* with experience in cardiovascular surgery and open-chest anesthesia is mandatory.

5. A *team* capable of performing *cardiac catheterization and angiocardiography,* conforming to the standards established by the report of the Committee on Cardiac Catheterization and Angiocardiography of the American Heart Association.[2]

6. A well-trained *pathologist,* familiar with the problems of the physiologist, the cardiologist and the surgeon, can assist the team in many ways. Extensive pathologic study should be made, if possible, on all patients who do not survive and the pathologic findings should be regularly reviewed by the whole group.

The Registry of Cardiovascular Pathology sponsored by the American Heart Association in cooperation with the Armed Forces Institute of Pathology, Washington 25, D. C., can supply pathologists and other members of the staff with material that may assist in the education of the physician in malformations of the heart, particularly those of surgical significance. The Institute will, upon request, also work up material if local facilities do not permit a thorough study.

B. Nurses

Outpatient and inpatient departments should have registered professional nurses familiar with the care of patients undergoing

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This report has been prepared by the Committee on Congenital Heart Defects of the Council on Rheumatic Fever and Congenital Heart Disease with the cooperation of the Executive Committee of the Council on Cardiovascular Surgery of the American Heart Association and reflects the Committees' findings in the matter under study.

This report serves to augment the *Recommended Standards for Cardiovascular Clinics.*[1]

diagnostic study and cardiovascular surgery. It is preferable that the *clinic* nurse have public health experience and be capable of assisting families to secure nursing supervision at home. The *hospital* nursing care must be under the close supervision of nurses familiar with needs of such cardiac patients. Expert and individual nursing care must be continued during the postoperative period for as long as it is medically advisable.

C. Medical Social Worker

A qualified medical social worker should be a full-time member of the staff. Medical social service should be available during *all* stages of care irrespective of economic status because of the anxiety, fear and worry in the family when cardiac surgery is considered. The case worker should be willing to aid in *all* social problems and must be experienced in the socioeconomic conditions usually found in such families—often young and inexperienced families. Both the medical social worker and the nurse (or public health nurse) should work together with the health and social agencies in the patient's community to establish optimum care for the patient.

II. Diagnostic Facilities

A. General

The following facilities, usually provided in a clinic, should be available:

1. Fluoroscopy and x-ray,
2. electrocardiography, and
3. a laboratory for routine analysis of blood and urine.

B. Special

The following special facilities are mandatory:

1. Bacteriology laboratory,
2. blood chemistry laboratory,
3. medication and oxygen at close hand for emergencies,
4. laboratory and equipment for cardiac catheterization, angiocardiography and aortography, conforming to the standards set by the Committee on Cardiac Catheterization and Angiocardiography;[2] this laboratory must be equipped for determination of oxygen saturation of blood. It is desirable also to have a cardiopulmonary laboratory, and
5. An experimental animal laboratory equipped and used for research and training in cardiovascular surgery.

III. Diagnostic Services to the Patient

A. Outpatient Department

In many instances, the diagnosis of the congenital cardiac defect can be established on an outpatient visit by means of a complete medical history, physical examination, fluoroscopic examination, x-ray, electrocardiogram and laboratory studies for blood and urine. The cardiologist should be able to fluoroscope all patients as a part of his examination.

B. Inpatient Department

It is well to recognize that some patients with congenital cardiac defects suffer from anoxemia, polycythemia or cardiac decompensation and require hospitalization and careful medical management during the period of diagnostic evaluation. Facilities for special diagnostic studies should be available to aid in a definitive diagnosis of all patients when necessary. Those patients in need of such studies as cardiac catheterization, angiocardiography or aortography should be hospitalized likewise for these procedures. It is preferable to have all diagnostic patients admitted to the medical or pediatric service of the medical center.

C. Teamwork

All members of the staff or team should work together in the evaluation of the patient's condition and in making decisions, but one staff physician should be solely responsible for the individual patient. The diagnostic team should have experience in the interpretation of cardiac catheterization findings in conjunction with the complete clinical picture; never should cardiac catheterization or angiocardiographic findings be considered alone. It is desirable to hold regularly scheduled *cardiovascular conferences* to discuss not only individual cases but also changes in general concepts of cardiovascular surgery.

IV. Basic Requirements in the Surgical Care of Patients

A qualified *surgeon* with training and experience in cardiovascular surgery, includ-

ing the use of arterial grafts, should be directly responsible for the surgical care of patients. He should have sufficient experience to meet with confidence the innumerable unusual situations that may arise.

There should be a full-time *resident* surgical and medical *staff* in the hospital, capable of dealing with all problems that arise following surgery.

Nursing supervision and care by *nurses* familiar with the needs of patients undergoing cardiovascular surgery are essential. It is highly desirable to have specialized nursing care provided in a recovery unit on a 24-hour basis. These nurses should be trained in the aftercare of patients undergoing cardiovascular surgery. Special nursing care should be given as long as it is medically advisable.

A *physician-anesthesiologist* who has had experience with patients undergoing cardiovascular surgery and open-chest anesthesia is mandatory.

Special equipment such as various types of needed oxygen apparatus, blood bank facilities, cardiac resuscitation or tracheotomy sets should be available through each 24 hours.

The operating room should be thoroughly equipped with all the advisable *surgical instruments* especially devised for intrathoracic and cardiovascular work as well as those commonly required for general surgery.

An intensive-care postsurgical unit must be open on a 24-hour basis to provide the special and constant care demanded by these patients.

The highly specialized staff and the facilities mentioned above are considered basic and are often not available outside a medical center that constantly cares for such patients.

V. Aftercare

A. Staff Care and Evaluation of Patient

It is essential that the medical staff at all times work closely with the surgeon and evaluate the results of surgery and the patient's cardiac reserve prior to discharge. Usually it is the responsibility of the cardiologist or pediatrician to assess the patient's cardiac reserve and to make recommendations concerning resumption of his activities.

The medical social worker and public health nurse should be available to assist with plans upon discharge of the patient from the hospital. They should follow through with referrals to the patient's local community, when indicated. The aim of both nurse and medical social worker should be to work together and to aid in follow-up planning, in order to achieve the best possible adjustment and rehabilitation of patient and family.

B. Contact with Referring Physician

The referring physician should be kept informed at all stages of the diagnostic study and care. He should be advised concerning:

1. The indications and recommendations for surgery,
2. the results of operation, including the occurrence of any postoperative complications and
3. the condition of the patient at the time of discharge from the hospital.

Recommendations for future medical management and follow-up after discharge are necessary for all cardiac patients.

C. Follow-up

It is advisable that the center request follow-up visits and send information so obtained to the referring physician to assist him in his future management of the patient. All diagnostic and surgical centers should carefully evaluate their operative results over a period of years.

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2. COURNAND, A., AND CO-WORKERS: Report of the Committee on Cardiac Catheterization and Angiocardiography of the American Heart Association. Circulation 7:769, 1953.

BOOK REVIEWS

Pulmonary Circulation. An International Symposium, 1958. Sponsored by the Chicago Heart Association. Edited by *Wright R. Adams, M. D.*, and *Ilya Veith*, Ph.D., New York, Grune & Stratton, Inc., 1959, 316 pages. $4.50.

This two-and-a-half-day symposium took place in Chicago in 1958. Thirty presentations were made, including a stimulating historical review by Dr. André Cournand. In addition to the physiology and pathology of the pulmonary circulation, the effects of lung disease, congenital heart disease, and acquired heart disease on the pulmonary circulation were also discussed.

The participants described many new technics for studying pulmonary circulation that undoubtedly will be productive in future investigations. Methods for measurement of instantaneous pulmonary capillary blood flow, volume of the pulmonary capillary bed, the collateral blood flow of the lung, and the normal and abnormal factors involved in pulmonary resistance were discussed. The chairmen of several of the sessions asked questions of the participants by way of introduction. That these questions were sometimes not answered or ignored detracts little from the value of the text but does indicate the lack of information concerning many aspects of the pulmonary circulation. The discussion of the papers was illuminating and frequently entertaining though necessarily abbreviated. If there was any omission in this symposium, it is concerned with the lack of materials describing studies of the pulmonary circulation by roentgen technics. This volume has been astutely edited and is certainly indispensable and interesting reading for all students of the pulmonary circulation.

MYRON STEIN, M.D.

Diagnosis of Congenital Heart Disease. Ed. 2. *Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe*, and *Bengt Jonsson*. Chicago, The Year Book Publishers, Inc., 1959, 866 pages, 727 illustrations. $28.00.

This second edition of an already established text now presents the detailed experience of the pediatric clinic of the Karolinska Sjukhuset in Stockholm with 742 cases of congenital heart disease investigated during the period 1951 to 1957. As compared to the first edition, the case material has been almost doubled, and, with the addition of 4 new chapters, extensive revision has been accomplished in order to bring both methodology and concepts up to date. The result is an improved text of the highest caliber—one of the very best in this field.

Each of 26 major types of congenital heart disease is considered in separate chapters, following 5 chapters devoted to a short review of basic embryology and roentgenologic anatomy of the heart, and of various diagnostic technics including such special methods as calibrated phonocardiography, exercise tests, electrokymography, cardiac catheterization, and angiocardiography. A valuable list of 727 pertinent references, with full titles, is also included.

The book is particularly outstanding for its treatment of angiocardiography with which the authors have had most extensive experience. A major proportion of 727 figures present angiocardiograms that cover the whole range of congenital cardiac abnormalities and that are so clearly reproduced as to render unnecessary the use of those explanatory drawings which, in other texts, often seem to be derived from the artist's imagination rather than from the companion angiocardiograms.

This text, ably translated from the Swedish, is an outstanding contribution to the subject, particularly suited to those cardiologists, radiologists, and cardiac surgeons who have special interest in the more advanced and definitive diagnostic aspects of congenital heart disease.

A. V. N. GOODYER, M.D.

Reminiscences and Adventures in Circulation Research. *Carl J. Wiggers.* New York, Grune & Stratton, Inc., 1958.

When a man retires after distinguished service, it is good for him to survey his career and see it in its entirety in the light of the wisdom which comes with the years. When such a person puts his survey into print, it makes fascinating reading, particularly if, as in the case of Wiggers, he has been a dominant force in the development of

the subject matter covered. Wiggers, furthermore, writes of an interesting period which burst upon the scene with great activity and has continued to expand with increasing velocity. His book gives him the opportunity to portray the personalities who had a major part in molding this exciting area of science and medicine. That he places his own associates and students in high relief is pardonable in so personalized a record of the events. The entire first section of the book devoted to reminiscences forms a vast landscape with selected events and persons spot-lighted against the general background. Wiggers' memory of episodes and people is amazing, aided no doubt by a careful examination of his collection of personal memorabilia. This remarkable recall the reviewer can vouch for. Many an event which he shared with Wiggers, and which he had forgotten, is reported in vivid (and accurate) detail.

People play a prominent role in the complicated process of creating new knowledge. Hence, these reminiscences should be very useful in characterizing those who had a part in it—and particularly the leading actor, Wiggers himself. This after all is an autobiography. Even the easy manner in which the subject is presented adds to its charm.

Having covered his reminiscences, the author then turns to a systematic review of his own hemodynamic studies from the vantage point of retrospection. The chapters devoted to this, summarize the present position of the author in the areas he has worked in. In this modern age of prolific publications it has been said that *even* the authors of scientific articles never re-read what they have written once they are published—that is really read to absorb the contents rather than just to scan. It is therefore of great importance and value to posterity for a man like Wiggers to calmly go over what he has accomplished and tie it all together. The reader will find it valuable to compare what Wiggers stresses with what he himself would stress. This part of the book is particularly timely since it forms a sound base upon which present and future work in hemodynamics can be founded. No one who works in circulation research or who bases his clinical work upon such research, nor any student or tyro, can therefore afford *not* to read these adventures carefully. The style is simple, the development of context is easy to follow, and the format and illustrations are clear. It is a "text book" written by the investigator who made the contributions. This kind of writing should become more fashionable. Perhaps once again Wiggers has pointed the way.

LOUIS KATZ, M.D.

Color Atlas and Management of Vascular Disease. *William T. Foley* and *Irving S. Wright.* New York, Appleton-Century-Crofts, Inc., 1959, 170 pages, 94 illustrations. $18.00.

The authors have written a simple, readable book devoted to the clinical management of disorders of the peripheral circulation. The material, based on the extensive experience of the authors and their associates at the Cornell Vascular Clinic, is presented lucidly and with brevity. The major emphasis is on the important details of practical medical therapy. The presentation leans heavily on abbreviated case histories, effectively supplemented by excellent colored photographs and roentgenograms. Adequate space is given to the conditions associated with vasospasm as well as to the organic arterial and venous diseases. This book is intended to be helpful to the practicing physician who does not have a special knowledge of the vascular diseases.

STANFORD WESSLER, M.D.

Klinische Methoden der Blutgerinnungsanalyse. *J. Jürgens, F. K. Beller,* und *M. Gänsslen.* Stuttgart, Georg Thieme, Verlag, 1959, 391 pages, 104 illustrations. $13.35.

The authors, distinguished investigators in this field, have prepared a comprehensive treatise that combines in an extraordinary way the physiology, physiopathology, clinical, clinical laboratory, and methodologic aspects of blood coagulation. They have acquitted themselves well in undertaking this formidable task in a succinct volume comprising 391 pages.

Their work will be found particularly useful not only by workers in this field but also by clinicians interested in hemostatic mechanisms, in coagulation, or in various phases of anticoagulant therapy in connection with their particular area of clinical competence.

The authors have managed to provide extraordinarily exhaustive bibliographic material, and have been most up to date in compilation of material, including most recent attempts at standardization of nomenclature. They have been extremely successful in presenting the large number of tests employed and recommended by individual workers in the field. Perhaps more important, the tests are presented in an orderly and editorially clear manner, sequentially in relation to the accepted phases of blood coagulation. Pertinent clinical phenomena are not neglected, either.

It is not surprising that some inaccuracies in bibliographic citation occur in view of the large volume of references cited, but this does not detract seriously from the value of the volume.

BENJAMIN ALEXANDER, M.D.

Milestones in Modern Surgery. *Alfred Hurwitz* and *George A. Degenshein.* New York, Paul B. Hoeber, Inc., 1958, 510 pages. $15.00.

This is an admirably written book, since its list of contributors is made up of the most distinguished names in modern surgery.

The authors set out to put together a collection of original articles, classics or "milestones" in the field, with prefatory remarks to supply perspective and a biographic sketch of each author to supply added interest. The book is further divided into 13 sections to cover a number of problems related to surgery, viz., Anesthesia, Hemostasis, Wound Healing, Cardiovascular Surgery, and so forth. Each section contains its comments, biographic sketches, and original papers.

The thought-provoking nature of the book, and, with a few exceptions, the classic aspects of its material make it a definite contribution to any medical library. The scope of the book can be appreciated by a partial listing of its contents. John Collins Warren describes his early experiences operating upon patients anesthetized with ether, Samuel J. Meltzer describes a workable system of endotracheal anesthesia, Edoardo Bassini describes his approach to repair of inguinal hernia while Theodor Bilroth, W. Ernest Miles, Franz Torek, and Evarts Graham each describes his classical surgical procedure. Sir Alexander Fleming's greatness emerges from his original description of his experience with penicillin.

Repeatedly as one reads the succinct and unassuming summations of the truly great, one is impressed by the fineness of the line between the recognition of a truly great novel or revolutionary idea and its almost complete disregard.

It is hoped that the authors will develop and expand this book so that its prefatory remarks will be more than cursory and therefore offer greater perspective. The total number of original papers included should be increased. This book has the concept and material to become an indispensable classic.

ANTHONY IMPARATO, M.D.

Differentialdiagnose innerer Krankheiten. Eine kurzgefasste Darstellung für Arzte und Studierende. *Robert Hegglin.* Stuttgart, Georg Thieme, Verlag, 1959, 819 pages, 517 figures, DM 79,50; $18.35.

This book of Dr. Robert Hegglin, Professor of Internal Medicine and Director of the Outpatient Department at the University of Zurich Medical School in Zurich, Switzerland, is a superb example of painstaking analysis and tabulation of widespread experience and knowledge. The first edition in 1952 was good proof of his ability to review critically the entire field of medicine. Systematically and logically he went over all the differential diagnostic problems of some of the most frequently seen signs and symptoms in order to describe them from an internist's point of view. Much emphasis was put on the interrelationship of the different specialties. Very skillfully he added the most important pathophysiologic and humoral-pathologic considerations. To help the more specialized reader recent methods and classifications and a well-selected bibliography were added to each chapter. In clear distinction to other more textbook-like works, the author avoided outlining syndromes with typical case histories. With this approach he was able to cover the most important organ systems in relation to internal medical diseases and, by mentioning briefly even very rare syndromes, he wrote an invaluable outline for the general practitioner and the inexperienced medical student as well as a useful guide for internists and lecturers. At the time the first edition came out such a concise abstract was badly needed for the German-speaking physician of Europe.

Only 1 year later a second edition appeared. In a way this was good evidence that this type of selecting and screening a vast material gained general approval. The chapters on "Headaches" and "Pains in the Extremities" were added although the basic format remained unchanged.

Further editions in 1954 and 1956 contained many supplements, the most recent references, and sections on "Lymphomas" and "Obstipation." The fifth edition of this very popular work was published in 1957. An increasing number of non-European authors were given credit in the text and in the bibliography.

Now the sixth edition has come out. Because it had grown considerably, it had to be revised and rearranged. While the basic concept remained the same, the chapter on "Icterus" has been entirely rewritten to include recent knowledge and newly developed viewpoints. A new section entitled "Paralysis of Voluntary Movements" with the most important neurologic considerations has been added.

Because of its very lucid, didactic presentation, this book, translated into Italian and Spanish, has found many enthusiastic readers. It is hoped that it will soon be published in English.

HANS J. SCHWEIZER, M.D.

Cardiovascular Collapse in the Operating Room. *Herbert E. Natof* and *Max S. Sadove.* Philadelphia, J. B. Lippincott Co., 1958, 197 pages, $6.00.

The authors of this volume present a concise yet comprehensive review of cardiovascular col-

lapse occurring in the operating room. Emphasis is placed throughout on the multiplicity of factors associated with this catastrophe.

In an analysis of 775 case reports derived from the literature, the following predisposing and precipitating causes are stressed: preoperative cardiovascular and pulmonary disease; operative hemorrhage; preoperative shock or hypovolemic states; severe infections; vomiting and aspiration; airway obstruction; and improper anesthetic technic. The mechanisms by which these factors adversely affect the anesthetized patient are discussed in detail. Particular attention is given to the pathophysiology of hypoxia and hypercapnia, the effect of surgery and anesthesia on myocardial function and the role of reflex changes.

To illustrate the multiple factors involved, 30 detailed case reports are presented of cardiovascular collapse occurring in the operating room at the University of Illinois Research and Educational Hospitals.

The authors emphasize the importance of careful preoperative evaluation and preparation of every surgical candidate with an aim to minimize those factors that predispose to collapse. Finally, the active treatment of cardiovascular collapse in the operating room is outlined.

This lucid analysis of a complex problem should be a valuable aid, not only to anesthetists and surgeons, but to all physicians.

ALLEN H. POSTEL, M.D.

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Differentialdiagnose innerer Krankheiten. Eine kurzgefasste Darstellung fur Arzte und Studierende. *Robert Hegglin.* Stuttgart, Georg Thieme, Verlag, 1959, 819 pages, 517 figures. DM 79, 50, $18.35.

Compendio di Elettrocardiografia. Ed. 2. *Vincenzo Masini.* Rome, Il Pensiero Scientifico, 1959, 474 pages, 200 illustrations. L. 4.500.

Should the Patient Know the Truth? A Response of Physicians, Nurses, Clergymen, Lawyers. Edited by *Samuel Standard* and *Helmuth Nathan.* New York, Springer Publishing Co., Inc., 159 pages. $3.00 hard cover, $2.00 soft cover.

A Clinical Introduction to Heart Disease. *Crighton Bramwell.* London, Oxford University Press, 1959, 229 pages, 61 illustrations. $5.50.

Clinical Evaluation of New Drugs. Edited by *S. O. Waife* and *Alvin P. Shapiro.* New York, Paul B. Hoeber, Inc., 1959, 223 pages. $7.50.

Fortschritte der Kardiologie—Advances in Cardiology. Vol. 2. Edited by *R. Hegglin* and *E. Lüthy.* Basel, S. Karger, 1959, 337 pages, 139 illustrations. sFr. 59.—

The Plasma Proteins. Clinical Significance. *Paul G. Weil.* Philadelphia, J. P. Lippincott Co. 1959, 133 pages. $3.50.

Biosynthesis of Terpenes and Sterols. Ciba Foundations Symposium. Edited by *G. E. W. Wolstenholme* and *Cecilia M. O'Connor.* Boston, Little, Brown and Co., 1959, 311 pages, 102 illustrations. $8.75.

Don't Worry About Your Heart. *Edward Weiss.* New York, Random House, 1959, 203 pages. $3.95.

Ergebnisse der Gesamten Tuberkulose-und Lungenforschung. *St. Engel, L. Heilmeyer, J. Hein,* and *E. Uehlinger.* Stuttgart, Georg Thieme, Verlag, 1959, 735 pages, illustrated. $34.40.

Electromyography in Nervous Diseases and in Magnesium Tetany. *N. Rosselle.* Louvain, Edouard Nauwelaerts, 1958, 159 pages, 183 illustrations. Paper bound $5.00, cloth bound $6.00.

Clinical Scalar Electrocardiography. *B. S. Lipman* and *E. Massie.* Ed. 4. Chicago, The Year Book Publishers, Inc. 1959, 474 pages, 339 illustrations. $8.00.

The Arterial Wall. Aging, Structure, and Chemistry. Edited by *Albert I. Lansing.* Baltimore, The Williams & Wilkins Co., 1959, 258 pages, illustrated. $7.50.

Konservative und chirurgische Behandlung angeborener und erworbener Herzfehler. *E. Derra, O. Bayer,* and *H. H. Wolter.* Stuttgart, Georg Thieme, Verlag, 1959, 64 pages, 25 illustrations. $1.55.

The Mediastinum. *Ted F. Leigh* and *H. Stephen Weens.* Springfield, Ill. Charles C Thomas, Publisher, 1959, 246 pages, 290 illustrations. $11.50.

Pädiatrischer EKG-Atlas. *Wilhelm Heck, Joachim Stoermer,* and *Gerhard Joppich.* Stuttgart, Georg Thieme, Verlag, 1959, 230 pages, 181 illustrations. $18.55.

Diagnosis of Congenital Heart Disease. Ed. 2. *Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe,* and *Bengt Jonsson.* Chicago, The Year Book Publisher, Inc., 1959, 866 pages, 727 illustrations. $28.00.

Atlas d'électrocardiographie et de vectocardiographie. *P. W. Duchosal* and *J. R. Grosgurin.* Basel, S. Karger, 1959, 181 pages, 44 illustrations. Frs. s. 23.—

Le Coeur. Tome II. *Camille Lian.* Paris, L'Expansion, 1959, 278 pages, 19 illustrations. 2,000 fr.

Chirugie der Arterien. *K. Kremer* and *Ernst Derra.* Stuttgart, Georg Thieme, Verlag, 1959, 280 pages, 150 illustrations. $14.05.

Color Atlas and Management of Vascular Disease. *William T. Foley* and *Irving S. Wright.* New York, Appleton-Century-Crofts, Inc., 1959, 170 pages, 94 illustrations. $18.00.

Transplantable and Transmissible Tumors of Animals. *Harold L. Stewart, Katherine C. Snell, Lucia J. Dunham,* and *Samuel M. Schlyen,* Washington, D.C., American Registry of Pathology, Armed Forces Institute of Pathology, 1959, 387 pages, 287 illustrations. $3.50.

Recent Advances in Cardiology. Ed. 5. *Terence East* and *Curtis Bain.* Boston, Little, Brown & Co., 1959, 421 pages, 133 illustrations. $10.00.

Carcinogenesis. Mechanisms of Action. Ciba Foundation Symposium. Edited by *G. E. W. Wol-*

Stenholme and *Maeve O'Connor*. Boston, Little, Brown and Co., 1959, 336 pages, 48 illustrations. $9.50.

Insulin Treatment in Psychiatry. Edited by *Max Pinkel* and *Harold E. Himwich*. New York, Philosophical Library, Inc., 1959, 386 pages. $5.00.

The Investigation of the Relative Function of the Right and Left Lung by Broncho-Spirometry. Technique, Physiology and Application. *Frank Bergan*. New York, Grune & Stratton, Inc., 1959, 145 pages, 85 illustrations. $4.50.

Reacciones elementales de la pared arterial frente a las injurias y en su relacion con la etipatogenia de la ateroesclerosis. *Emiliano Roda Pérez*. Lima, Universidad Nacional Mayor de San Marcos, 1958, 345 pages, illustrated.

Klinishe Methoden der Blutgerinnungsanalyse. *J. Jürgens, F. K. Beller,* and *M. Gänsslen*. Stuttgart, Georg Thieme, Verlag, 1959, 391 pages, 104 illustrations. $13.35.

Semeiologia Fonocardiografica. *G. Gigli* and *G. Muiesan*. Rome, Il Pensiero Scientifico, 1959, 361 pages, 261 illustrations. L. 6,000.

Atlas intracardialer Druckkurven. *Otto Bayer, Hans H. Wolter, G. R. Graham,* and *E. Low-Maus*. Stuttgart, Georg Thieme, Verlag, 1959, 179 pages, 55 illustrations. $16.20.

Der menschliehe Herzschlag. Neue Forschungsergebnisse. I. Teil. *Franz A. N. Kienle*. Frankfurt am Main, Wolfgang Weidlich, Verlag, 1958, 114 pages, 212 illustrations. DM 39,80.

Herz-Kreislauferkrankungen. Pathologische Physiologie und Funktionelle Therapie. Vol. 1 & 2. *M. Hochrein* and *I. Schleicher*. Darmstadt, Dr. Dietrich Steinkopff, Verlag, 1959, 2196 pages, 580 illustrations. DM 230,—

Mitral Valvulotomy. Ed. 1. *Harold J. Stewart* and *Frank Glenn*. Springfield, Ill., Charles C Thomas, Publisher, 1959, 244 pages, 25 illustrations. $10.50.

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La prova ipossica e la prova da sforzo nella diagnosi delle coronaropatie. *C. Candiani* and *C. Fauda*. Firenze, Edizioni Mediche Italiane, 1959, 87 pages, illustrated.

Atelectasia Pulmonar. I. Conceito. II. Fisiopatologia Circulatória. *Robalo Cordeiro*. Portugal, Coimbra, 1959, 518 pages, 154 figures.

Antithrombotic Therapy. *Paul W. Boyles*. New York, Grune & Stratton, Inc., 131 pages, illustrated. $5.00.

Acute Cardiac Pulmonary Edema. *Sigmund Wassermann*. Springfield, Ill., Charles C Thomas, Publisher, 1959, 123 pages. $4.25.

Diseases of the Chest Including the Heart. Edited by *J. Arthur Myers*. Springfield, Ill., Charles C Thomas, Publisher, 1015 pages, illustrated. $34.50.

Metabolic Aspects of Renal Function. *William D. Lotspeich*. Springfield, Ill., Charles C Thomas, Publisher, 1959, 214 pages, 58 figures. $7.50.

Elektroanatomie des menschlichen Herzens. *Franz A. N. Kienle*. Frankfurt am Main, Wolfgang Weidlich, Publisher, 1959.

The Acute Medical Syndromes and Emergencies. *Albert Salisbury Hyman,* with the collaboration of *Samuel Weiss, George Guttman Ornstein, Howard F. Root, Anna Ruth Spiegelman,* and *Jack Abry*. New York, Landsberger Medical Books, Inc., 1959, 442 pages. $8.75.

Work and the Heart. By 93 Authors. Edited by *Francis F. Rosenbaum* and *Elston L. Belknap*. New York, Paul B. Hoeber, Inc., 1959, 537 pages, illustrated. $12.00.

Pathology of the Heart. Ed. 2. Edited by *S. E. Gould*. Springfield, Ill., Charles C Thomas, Publisher, 1959, 1138 pages, illustrated. $32.50.

Electrical Impedance Plethysmography. The Electrical Resistive Measure of the Blood Pulse Volume, Peripheral and Central Blood Flow. *Jan Nyboer*. Springfield, Ill., Charles C Thomas, Publisher, 1959, 243 pages, 104 figures. $7.50.

Arterial Embolism in the Limbs. *A. L. Jacobs*. Baltimore, Williams & Wilkins Co., and Edinburgh and London, E. and S. Livingstone Ltd., 1959, 200 pages, illustrated. $8.00.

Acute Pericarditis. David H. Spodick. New York Grune & Stratton, Inc., 1959, 182 pages, illustrated. $6.50.

Cinefluorography. Edited by *George H. S. Ramsey, James S. Watson, Jr., Theodore A. Tristan, Sydney Weinberg,* and *William S. Cornwell*. Springfield, Ill., Charles C Thomas, Publisher, 1959, 266 pages, illustrated. $11.75.

Die Regulation der Natrium- und Wasserausscheidung. *Michael Földi* and *Georg Szabó*. Budapest, Akadémiai Kiadó, 1959, 267 pages, illustrated.

Angiologie, Pathologie, Klinik und Therapie der peripheren Durchblutungsstörungen. *Max Ratschow*. Stuttgart, Georg Thieme, Verlag, 1959, 831 pages, 373 figures. DM 174.—

ABSTRACTS

ATHEROSCLEROSIS

Altschul, R.: Influence of Cytochrome C and Hematoporphyrin on Serum Cholesterol. Ztschr. Kreislaufforsch. **48**: 844 (Sept.), 1959.

Injection of 0.02 to 0.04 Gm. of cytochrome C in rabbits caused a highly significant decrease in serum cholesterol, which usually returned to previous values within 24 hours. This was attributed to increased oxidation of cholesterol due to cytochrome C. Intramuscular injection of 1 to 20 mg. of hematoporphyrin, which is contained in the nucleus of cytochrome, also caused a highly significant decrease of cholesterol persisting also after 24 hours. Oral medication was without effect.

LEPESCHKIN

de Soldati, L., Stritzler, G., Balassanian, S., and Bourguet, M. D.: Effect of Nicotinic Acid on Blood Lipids in Arteriosclerotic Patients. Cardiologia **35**: 84, 1959.

In 37 arteriosclerotic patients, aged 36 to 75, the total blood lipids and fatty acids were found to be elevated in all. Cholesterol levels were beyond normal limits in 26, lipid phosphorus was increased in 2, phospholipids were elevated in 4 patients, and mean beta-lipoproteins and beta/alpha lipoprotein index were increased. These patients were given 1 to 4 Gm. of nicotinic acid by mouth daily during periods of 5 days to 4 months with the dietary habits unchanged during the time of study. Striking reductions of blood lipid levels were observed in patients with high cholesterol levels prior to treatment, with particular reduction of the total cholesterol, cholesterol esters, and fatty acids. In patients with normal cholesterol levels there was no significant reduction of blood lipids. The mean beta/alpha lipoprotein index was moderately reduced. Side effects, notably flushing and itching on the face and upper extremities, led to the suspension of the drug in 10 per cent of patients but actual harmful effects were never seen. The interruption of treatment was generally followed by an increase in the blood lipid levels. The administration of large doses of nicotinic acid seemed to be effective in reducing high blood lipid levels in arteriosclerotic patients without dietary restrictions.

BRACHFELD

Dodds, C., and Mills, G. L.: Influence of Myocardial Infarction on Plasma-lipoprotein Concentration. Lancet **1**: 1160 (June), 1959.

The lipoprotein patterns in men at various intervals after acute infarction (24 hours to 8 weeks) were compared with the values for healthy men as estimated by ultracentrifugation, Cohn fractionation, and paper electrophoresis. In general, the younger patients with coronary artery disease had higher lipoprotein levels than the elderly. The latter tended toward normal. Following an infarction there was a profound disturbance of the equilibrium of lipoprotein metabolism, which caused the lipoprotein levels to vary widely at different times. There was a slight decrease in the content of cholesterol in alpha lipoprotein, which was far outweighed by an increase in the percentage of cholesterol in beta lipoproteins. There was a sharp drop in the concentration of total cholesterol and the cholesterol percentage in beta lipoprotein starting a day or

so after the acute infarction. Then there was a slow climb until the previous level was reached at about 3 to 5 weeks. Detailed analysis of the lipoprotein distribution by the ultracentrifuge showed that in each Sf range there was a rise in concentration reaching a peak value at about 4 weeks. These results support the hypothesis that a lipid abnormality is associated with myocardial infarction, and makes it clear that the lipoprotein pattern during the first 2 months of illness is constantly changing and cannot be represented by a single measurement during this period. It is, therefore, unwise to base conclusions on a comparison of patterns after infarction with those of a separate group of controls until sometime after the eighth week. It is suggested that the preliminary fall in lipid levels after infarction is an immediate consequence of the "stress." The largest postinfarction variations in lipid level were observed in patients whose preinfarct level was high; those with a low level showed little or no change.

SHEPS

Dole, V. P., James, A. T., Webb, J. P. W., Rizack, M. A., and Sturman, M. F.: The Fatty Acid Patterns of Plasma Lipids during Alimentary Lipemia. J. Clin. Invest. **38**: 1544 (Sept.), 1959.

The plasma lipids were analyzed in a group of normal subjects in the fasting state and for a 9-hour period after a single meal consisting of 100 Gm. of corn oil, coconut oil, or butter. The plasma lipids were fractionated into chylomicra, nonesterified fatty acids, triglycerides plus cholesterol esters, and phospholipids. For each of these fractions the fatty acid composition was determined with gas-liquid chromatography. In the fasting samples, the fatty acid composition of each of the fractions revealed a fairly consistent pattern in the group of normal subjects. The absorption of corn oil, coconut oil, or butter failed to alter significantly the fatty acid composition of the lipid fractions when measured at ½, 1, and 2½ hours (short-term studies) or at 3, 6, and 9 hours (longer-term studies). The coconut oil had mainly saturated fatty acids, whereas the corn oil contained mostly unsaturated fatty acids (89 per cent). The stability of chylomicra in plasma was striking and suggested that they were in equilibrium with a larger pool of tissue lipids. These studies were concerned mainly with the transport of fat after an acute load. Studies in which a distinctive fat was fed for many weeks altered the composition of tissue lipids, and this change may be reflected in the plasma of the fasting subject.

KAYDEN

Fischer, F. W.: Serum Lipoproteins. Ztschr. Kreislaufforsch. **48**: 517 (June), 1959.

Nearly all serum lipids exist normally in the form of lipoproteins. In young persons (18 to 35 years of age), beta lipoproteins exceed 60 per cent in less than one half of the women but in three fourths of the men, corresponding to the difference between the sexes in the clinical incidence of atherosclerosis. Of 4,546 patients with clinical atherosclerosis, 90 per cent had values exceeding 72 per cent, the upper range in young women. A value exceeding 80 per cent was found in two thirds of the patients with several myocardial infarctions but in only one third of those with a single infarction. The concentration of beta lipoproteins, expressed as a percentage of the total, seemed to be a more sensitive criterion than their absolute concentration or the concentration of total lipids. While in large statistical groups this concentration showed definite correlation to the clinical findings and life-expectancy, its individual prognostic significance was small.

LEPESCHKIN

Friedman, M., and Byers, S. O.: Evaluation of Nicotinic Acid as an Hypocholesteremic and Anti-Atherogenic Substance. J. Clin. Invest. **38**: 1328 (Aug.), 1959.

The addition of nicotinic acid to the diet of rats produced a moderate decline in serum cholesterol as compared to that of controls at the end of 12 days. The treated rats, however, failed to gain weight. They were able to absorb cholesterol and total lipid as well as control rats. The daily biliary excretion of cholesterol remained the same for the experimental and control series. There appeared to be no effect, therefore, upon the intestinal absorption of cholesterol or total lipid, or upon the hepatic synthesis of cholesterol in rats given nicotinic acid. A group of rats given nicotinic acid and a high fat-cholesterol diet in limited amount developed the same degree of hypocholesteremia as their controls, who were also fed the high fat-cholesterol diet in like limited amounts. The anoretic properties of nicotinic acid may have been responsible for the hypocholesteremic effect previously noted in animal experiments. Rabbits pair-fed on high fat-cholesterol diets with and without nicotinic acid failed to exhibit a significant difference either in their average plasma cholesterol or in their degree of aortic atherosclerosis. The authors suggest that subtle changes in quality and quantity of the foods ingested by subjects receiving nicotinic acid may, in part, be responsible for the hypocholesteremic action.

KAYDEN

Groom, D., McKee, E. E., Webb, C., Grant, F. W., Pean, V., Hudicourt, E., and Dallemand, J.: Coronary and Aortic Atherosclerosis in the Negroes of Haiti and the United States. Ann. Int. Med. **51**: 270 (Aug.), 1959.

The degree of coronary and aortic atherosclerosis in 128 autopsies of Haitian Negroes and 139 autopsies of American Negroes was estimated by a grading scale. Routine autopsies covering all types of mortality over age 20 were utilized as representative samples of the 2 population groups. The degree of atherosclerosis in the coronary arteries of the hearts of the American subjects was almost double that of Haitian subjects, but no such difference was noted in the corresponding aortas. This was true for both men and women, and at virtually all age levels. Coronary grades of male subjects from both countries increase similarly with age to a suggested leveling in the fifth decade; those of the females appeared to increase uniformly from the lowest values to the highest at 60 and beyond. An attempt was made to gather data on the dietary habits of the 2 groups as well as economic and work statistics. The inaccuracy of vital statistics for comparing the incidence of coronary disease in the 2 different civilizations was stressed. The apparent predisposition of the American group to coronary but not to aortic atherosclerosis suggested that factors other than diet alone must play important roles. The authors suggest that some of these factors may be the more stressful environment, the greater complexity, mechanization, education, and competitiveness of the Negro's life in the United States.

KAYDEN

Holman, R. L., Blanc, W. A., and Andersen, D.: Decreased Aortic Atherosclerosis in Cystic Fibrosis of the Pancreas. Pediatrics **24**: 34 (July), 1959.

Lipid accumulations in the aorta were studied in necropsy specimens from 18 patients with cystic fibrosis of the pancreas and from 21 control patients all between the ages of 6 and 13 years; all of the patients were Caucasians. The authors found that the average percentage of the intimal surface involved was over 4 times as great in the control group as compared to the group with fibrocystic disease. They reviewed the metabolic abnormalities found in patients with fibrocystic disease but were unable to come to any satisfactory conclusions as to the etiologic factors involved in producing such a strong relationship between this disease process and atherosclerosis.

KARPMAN

Kuo, P. F., and Carson, J. C.: Dietary Fats and the Diurnal Serum Triglyceride Levels in Man. J. Clin. Invest. **38**: 1384 (Aug.), 1959.

The serum lipids were measured in 6 patients with the following lipid abnormality: 2 patients with hypercholesteremia; 2 patients with essential hyperlipemia; 2 patients with hypercholesteremia and mild hyperlipemia. Four other patients without any known lipid abnormalities were also studied as normal controls. Diurnal variations in serum cholesterol and phospholipid levels were minimal in the 10 subjects whether on isocaloric full diet, rice and fruit, or corn oil formula diets in which corn oil constituted 50 to 70 per cent of the total daily caloric intake. In the 4 normal patients and 2 patients with hypercholesteremia, the postprandial serum triglyceride elevations were lower and briefer while on the corn oil diet than on a full diet. However, the differences in the effects of unsaturated and saturated dietary fats upon the postprandial serum triglyceride concentrations become progressively less evident in the 4 patients with increasingly severe degrees of hyperlipemia. On rice and fruit diets the fasting serum triglycerides of the nonlipemic subjects were only slightly higher than their respective fasting levels measured during the full and the corn oil dietary periods. In the hyperlipemic patients, significant increases in their fasting triglyceride concentrations were observed, following the change from high-fat diets (100 to 140 Gm. animal fat) to the rice and fruit diet (5 Gm. fat). The mechanism of the fasting lipemia with rice diet is not understood, but patients with ischemic heart disease should certainly not be placed on a rigidly restricted fat diet.

KAYDEN

Pick, R., Stamler, J., Rodbard, S., and Katz, L. N.: Effects of Testosterone and Castration on Cholesteremia and Atherogenesis in Chicks on High-Fat, High-Cholesterol Diets. Circulation Research **7**: 202 (Mar.), 1959.

These experiments explored the effects of androgenic activity on atherogenesis in chicks using a standardized high-fat, high-cholesterol diet. Testosterone in large doses partially inhibited hypercholesteremia but no effect was noted on aortic or coronary atherogenesis. Gonadectomy in young male and female chicks was without influence on hypercholesteremia and atherogenesis.

PAUL

Worne, H. E., and Smith, L. W.: Effects of Certain Pure Long Chain Polyunsaturated Fatty Acid Esters on the Blood Lipids of Man. Am. J. M. Sc. **237**: 710 (June), 1959.

The role of polyunsaturated fatty acids in the etiopathogenesis of hypercholesteremia is discussed. Various polyunsaturated fatty acids were administered to patients with and without hyperlipemia. Studies were carried out over a period of 90 days. There was a significant correlation between the number of double-bonds in the fatty acid molecule and their effect on the blood lipids. Four grams per day of the 4, 5, and 6 double-bonded fatty acids, produced significant changes in blood lipid reflected by reduced cholesterol levels and a more favorable cholesterol-phospholipid ratio. Sixteen grams of 2 and 3 double-bonded fatty acids per day produced the same effect, although 4 Gm. per day was without effect. A combination of all the polyunsaturated fatty acid esters gave rise to the same effects as the pure individual esters. In several patients with skin xanthomata, elimination of these lesions was observed concurrent with reduction of the accompanying hyperlipemia or hypercholesteremia. Patients exhibiting signs of angina and intermittent claudication showed objective evidence of gradual clinical improvement as the blood lipids were reduced to normal levels.

SHEPS

Zemplenli, T., and Grafnetter, D.: Fatty Acid Release on Incubation of Lipemic Serum with Rat Tissues. The Influence of Heparin and Fasting. Arch. int. pharmacodyn. **122**: 57 (Oct.), 1959.

Tissue pulp from rat heart, lung, fat tissue, liver, brain, and striated muscle was incubated with lipemic human serum, and lipolysis was followed by estimating freed unesterified fatty acids. Except for brain and muscle, which showed only slight activity, marked lipolysis was found with all the above tissues, which was strongly enhanced in the heart and lung when incubated with 1.6×10^{-5} M heparin. Lipolytic activity of perirenal fat was not always increased by heparin. Lipolysis of mesenteric fat was enhanced by heparin to a significant degree only in the fasted animal. The increase in activity in the presence of heparin and the results of experiments in the presence of inhibitors are in agreement with the assumption that there is a close relationship between this tissue enzymatic system and lipoprotein lipase or "clearing factor."

BRACHFELD

BLOOD COAGULATION AND THROMBOEMBOLISM

Borchgrevink, Chr. F.: Myocardial Infarction in a Haemophiliac. Lancet **1**: 1229 (June 13), 1959.

A 68-year-old man sustained an acute posterior myocardial infarction after 10 years of angina pectoris. There was a history of a tendency to secondary bleeding. Laboratory tests of the hemostatic mechanism revealed antihemophiliac A factor level of 16 per cent. Six of the male relatives also had similar levels of this factor. This is the third reported case of myocardial infarction in a hemophiliac. Anticoagulant therapy was started but was discontinued when the bleeding diathesis was diagnosed.

SHEPS

Boyles, P. W., Jones, R., Jr., and Nichol, E. S.: Effect of Phospholipid Fractions upon the Coagulation Defects in Patients on Long-Term Dicumarol Therapy. Blood **14**: 781 (June) 1959.

The relatively frequent occurrence of bleeding in patients on a long-term anticoagulant regimen stimulated this study of the coagulation defects following administration of Dicumarol over prolonged periods. In addition to the effects of Dicumarol on the prothrombin conversion factors, long-term use of this drug caused a defect in thromboplastin and in thrombin generation. The use of a preparation of brain or soybean phospholipids corrected the abnormal coagulation time and the thrombin generation test of patients on long-term Dicumarol therapy. Deficiency in thromboplastin generation of these patients was not corrected.

KITCHELL

Gold, H., and Lilley, G. W.: New Anticoagulant for Oral Use-3-(l'-Phenylpropyl)-4 Hydroxycoumarin (Liquamar). J.A.M.A. **170**: 1303 (July 11), 1959.

One hundred and eleven patients received short-term anticoagulant therapy with 3-(l'-phenylpropyl)-4 hydroxycoumarin (Liquamar). Some received heparin and Liquamar combined. After a 30-mg. loading dose, a prophylactic or therapeutic response was obtained within an average of 42 hours in 77 per cent of the patients after this induction period. A 6.4-mg. (average) maintenance dose resulted in protective prolongation of prothrombin times in 88 per cent of patients within 66 hours after the administration of the loading dose. Maintenance doses varied between 1.5 and 12 mg., with an average of 4.0 mg. A smaller (21 mg.) loading dose was indicated if the initial prothrombin time was above the nor-

mal. Because of the induction period, heparin could also be given if an immediate anticoagulant effect was desired. Hematuria and 1 subconjunctival hemorrhage were the complications that occurred in 3.6 per cent of cases; all recovered. Vitamin K_1 orally or parenterally corrected "overshooting" (prothrombin time greater than 40 seconds) or bleeding.

KITCHELL

Johnson, A. J., and McCarty, W. R.: The Lysis of Artificially Induced Intravascular Clots in Man by Intravenous Infusions of Streptokinase. J. Clin. Invest. **38**: 1627 (Sept.), 1959.

A highly purified preparation of streptokinase (SK) was infused intravenously to produce intravascular clot lysis in human subjects. Blood clots from 5 to 20 cm. long were produced in peripheral veins of volunteers by direct irritation of the intima with a dental broach or by chemical irritation with sodium morrhuate. A total of 38 blood clots was produced, 13 in the control series and 25 in the treated series. Spontaneous lysis did not occur in any of the 13 subjects. The methods of giving SK intravenously may be divided into 3 groups, depending on amount of initial SK infused and subsequent infusions. In Method P, the priming dose of SK allowed for neutralization of each patient's SK antibody and inhibitors of SK plasmin, with a large amount of circulating free plasmin. Subsequent small doses of SK, 25,000 to 50,000 units per day, sufficed to produce large amounts of plasmin. This method was ineffective in 7 instances. In Method SK, the priming dose again neutralized antibody and inhibitor, but first sustaining doses of 100,000 to 300,000 units of SK in 1 to 3 hours reduced plasminogen sharply and prevented any excessive amounts of plasmin. In this method free SK or activator was made available in the blood by the continuous infusion of 45,000 to 65,000 units per hour. This procedure was effective in 2 patients, partially effective in 3, and ineffective in 2. In Method SK-P, priming and first sustaining infusions were similar to Method SK, but the second sustaining dose of SK was infused at 25,000 to 45,000 units per hour to provide plasmin and free SK or activator without excessive depletion of plasminogen. In 11 vein clots persistent clot lysis was achieved in all 11. The method involved frequent determination of patient's plasminogen, plasmin, free SK, plasmin-activator and prothrombin time to determine rates of infusion. Clots established for 48 hours were more difficult to lyse than 24-hour clots.

KAYDEN

McDonald, L., and Edgill, M.: Changes in Coagulability of the Blood during Various Phases of Ischaemic Heart-Disease. Lancet **1**: 1115 (May 30), 1959.

Coagulability of the blood as estimated by platelet count, platelet stickiness, fibrinogen estimation, thromboplastin-generation and prothrombin time (Russell's viper venom, Stypven), was compared in 22 healthy men; 30 men with angina pectoris, 7 with acute coronary insufficiency, and 10 with cardiac infarction. Values for platelet stickiness, thromboplastin-generation, and fibrinogen estimation significantly increased from healthy controls to patients with angina, and from these to patients with infarction. Findings in acute coronary insufficiency were not significantly different from those with angina pectoris except that the platelet count was higher in this group. There was no other significant difference between groups in respect to platelet counts. The coagulability of the blood was higher in patients with angina than in the healthy controls and higher again in patients with cardiac infarction. Patients with acute coronary insufficiency appeared to have a level of coagulability comparable to those found in patients with angina. Repetition of these tests at intervals in certain of these patients showed unaltered results. Unpublished data apparently suggested that the increased coagulability associated with cardiac infarction was greatest 1 or 2 days after infarction and gradually returned to the level found in patients with angina pectoris who had not had recent infarction. It is concluded that there is clear evidence of phasic hypercoagulability when the blood of patients with ischemic heart disease is studied in vitro. This is entirely in keeping with a variable hyperthrombotic state and the fact that ischemic heart disease is marked clinically by episodes of thrombosis.

SHEPS

Perlow, S.: Embolism at Bifurcation of Aorta. J.A.M.A. **171**: 41 (Sept. 5), 1959.

Twenty-three cases of embolism at the aortic bifurcation are reviewed. Diagnosis is not difficult if the doctor is aware of the possibility in patients with atrial fibrillation, mitral valvular disease, or recent myocardial infarction. Embolism can occur with other conditions such as bacterial endocarditis, pulmonary vein thrombosis, aneurysm of the aorta, and atheromatous plaques, as well as the very rare case following paradoxical embolism. The most important therapy is immediate heparinization to prevent thrombus progression with closure of the collateral channels. This should be done prior to tran-

porting patients to the hospital. Vasodilating drugs and lumbar sympathetic anesthetization have a questionable value. Transabdominal aortic embolectomy should be performed as soon as possible in all patients whose general condition will permit. It may be successful even in a late stage.

KITCHELL

Rawls, W. B., and Connor, A. R.: Long Term Anticoagulant Therapy. A Six-Year Study of an Indandione Derivative. Am. J. Cardiol. **4**: 470 (Oct.), 1959.

The anticoagulation effects of phenindione (Hedulin) were observed in over 300 hospitalized and ambulatory patients, most of whom had myocardial infarction or peripheral vascular disease. Therapy periods ranged up to 3 years in the individual patient while the whole study extended from 1952 to 1958. The drug was administered daily, usually in divided doses, aiming to maintain a prothrombin time 1½ to 1¾ times the control level. The dosage varied from patient to patient, but the individual's maintenance dose was quite constant and required prothrombin-time determinations about every third week. Two significant bleeding episodes were noted; prothrombin levels at the time were not given; nor was any mention made of possible therapeutic benefits from the anticoagulation.

ROGERS

Rodman, T., Ryan, C. S., and Pastor, B. H.: A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs. I. Properties. Am. J. Med. **27**: 411 (Sept.), 1959.

A comparative study was undertaken in 80 subjects of 4 commonly used and representative prothrombinopenic drugs, bishydroxycoumarin, warfarin, pherinidene, and diphenadione, in order to obtain data on onset of action, peak effect, duration of action, and variability of effect. The onset of action of all was between the eighth and sixteenth hour after a single, large dose. Peak effect of pherinidene was in 32 hours and, of the others, was 40 hours. Duration of effects was variable but extent of depression was relatively uniform among subjects.

KURLAND

Rodman, T., Ryan, C. S., Pastor, B. H., and Hollendonner, W. J.: A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs. II. Clinical Study. Am. J. Med. **27**: 415 (Sept.), 1959.

Four thrombinopenic agents were compared in 287 patients. It was noted that with large initial doses more rapid depression of prothrombin levels could be achieved, yet at 16 hours few patients could be brought into therapeutic range and at 64 hours most levels were satisfactory with any drug. When facility with which patients could be kept in therapeutic range was measured, bishydroxycoumarin was slightly better than diphenadione and much better than pherinidene and warfarin. Satisfactory control was achieved in the majority of patients with all 4 drugs. There was relatively wide variation in dosage requirements in the same patient from day to day and among patients receiving the same preparation. None of the 4 drugs studied appeared to have enough advantages over the others to be considered as the prothrombinopenic agent of choice.

KURLAND

Stein, I. D.: Management of Thrombophlebitis with Phenylbutazone. Am. J. Cardiol. **4**: 476 (Oct.), 1959.

Thrombophlebitis in 785 patients was treated by administering oral phenylbutazone to a total of 3 Gm. in 1 week or less. The 706 cases with the superficial type were managed as out-patients, and some received additional local or anticoagulant therapy with a minimum of bed rest. Of the 79 patients having deep phlebitis, the majority were hospitalized and given anticoagulants; then phenylbutazone was begun about a week later because of unsatisfactory progress. In both the superficial and deep cases, improvement ordinarily was noted 12 to 24 hours after beginning phenylbutazone, and complete resolution was described in 96 per cent of each group. Dyspepsia was troublesome in 5 per cent of patients and dermatitis or generalized edema developed in 0.5 per cent each; no serious side effect from the drug was observed. Phenylbutazone therapy for 1 week is recommended both for superficial and deep thrombophlebitis; in the deep type, anticoagulants and elastic stockings are also advised.

ROGERS

Stevens, H., and Ammerman, H. H.: Intracranial Venous Thrombosis in Early Pregnancy. Am. J. Obst. & Gynec. **78**: 104 (July), 1959.

Two cases of intracranial venous thrombosis during the first trimester of pregnancy are described. Both patients had headache, stupor, increased intracranial pressure, and progressive development of focal neurologic manifestations. Cerebral veins were occluded in one, and a life-saving craniotomy was performed for decompression. A Torkildsen procedure in the second patient, whose lesion was in the posterior fossa, was followed by prompt recovery. Full-term normal

infants were delivered in both cases. Because the clotting tendency is increased and the fibrinogen level raised in pregnancy, this condition should be considered when rapidly developing focal neurologic signs occur in any month of pregnancy.

MAXWELL

Sullenberger, J. W., Anlyan, W. G., and Weaver, W. T.: Serotonin in Intravascular Thrombosis. Surgery **46**: 22 (July), 1959.

The occasional observation of vasospastic phenomena in patients with thrombotic disease led to a study investigating possible increased serotonin activity resulting from the induction of thromboses. The intravenous infusion of thrombin or of thromboplastin into anesthetized dogs was followed by an immediate increase up to 4-fold in 5-hydroxyindoleacetic acid (5-HIAA—a serotonin derivative) urinary excretion which continued for 6 hours or more. Also there was a prompt but brief decrease in the number of circulating platelets. Twenty-four hours later, pulmonary thrombi could be seen. Control animals receiving saline infusions showed no significant alteration in 5-HIAA excretion or platelet count. The infusion of 20 mg. of hydrocortisone was followed by a slight rise in 5-HIAA excretion but no change in platelet count. On the other hand, the stress of various types of clinical surgery was attended by a decrease of 5-HIAA for 2 to 3 days postoperatively; this decrease was not attributed to oliguria. It was concluded that in vivo blood coagulation results in a significant elevation of blood serotonin, but whether the serotonin is related to accompanying vasospastic phenomena is speculative.

ROGERS

Torre, J. M., Macias, J. J., and Velazquez, T.: Thromboembolic Accidents of the Lung. Arch. Inst. cardiol, México **29**: 385 (July-Aug.), 1959.

Fifty-five cases of thromboembolic phenomena in the lung (including thromboses, emboli, and infarctions) found among a series of 453 autopsies at the "Hospital Central" of San Luis de Potosi were analyzed. In 19 cases, these phenomena were the cause of death. The difficulties in establishing a true clinical diagnosis were noted. Only 22.5 per cent of the cases were diagnosed correctly. The clinical picture considered as typical of infarction of the lung was present only in 28.5 per cent of the cases. Twenty-four of the patients had heart disease (43 per cent). In these 24 patients, the occlusive process of the lesser circulation produced a pulmonary infarction in 100 per cent of the cases while in the noncardiac patients only this was present in 38 per cent. The circumstances that favor the appearance of pulmonary infarction in noncardiac patients are discussed. Sudden death was the only manifestation of the disease in 4 patients (7 per cent).

BRACHFELD

CONGENITAL ANOMALIES

Bayer, O., Wolter, H. H., and Bachmann, D.: Evaluation of Pulmonary Hypertension in Congenital Heart Disease with Left to Right Shunt. Ztschr. Kreislaufforsch. **48**: 243 (Mar.) 1959.

In atrial septal defect, where the shunt takes place at low pressure, pulmonary hypertension is usually absent in the beginning and develops gradually as a result of a secondary increase in pulmonary vascular resistance. Unless the defect is unusually large, a high pulmonary arterial pressure exceeding 70 mm. makes a high operative mortality and failure of pulmonary hypertension to regress after operation probable. On the other hand in a shunt at high pressure as in large ventricular septal or aortico-pulmonary defects, marked pulmonary hypertension is a direct consequence of the defect and shows no progression, whereas secondary increase of pulmonary vascular resistance leads to reversal of the shunt and late cyanosis. The degree of regression of pulmonary hypertension after operation is accordingly greatest in patients with the most marked hypertension. If the communication is small, as in persistent ductus, marked pulmonary hypertension may result either from secondary increase of pulmonary resistance or from persistence of the high resistance that is normal for fetal life. In this case the mortality during operation is much greater with marked pulmonary hypertension, and the degree of regression after operation is smaller.

LEPESCHKIN

Burch, G. E., and DePasquale, N.: The Spatial Vectorcardiogram in Proved Congenital Atrial Septal Defect. Am. Heart J. **58**: 319 (Sept.), 1959.

Conventional electrocardiograms and spatial vectorcardiograms with the equilateral tetrahedral reference system were recorded on 20 patients with atrial septal defect proved by cardiac catheterization, operation, or autopsy. The QRS$_{s}$ loops of the patients with ostium primum defects were oriented to the left, superiorly, and posteriorly, and rotated counterclockwise. With ostium secundum defects the loops were oriented to the right, inferiorly, and anteriorly, and rotated

clockwise. The vectorcardiographic findings in each type of defect were consistent and the differences between the 2 groups readily recognized, so that the vectorcardiogram was found to be useful in the diagnosis of atrial septal defect.

SAGALL

Connor, A. C., McFadden, J. F., Houston, B. J., and Finn, J. L.: Familial Congenital Complete Heart Block. Am. J. Obst. & Gynec. **78:** 75 (July), 1959.

The literature on congenital complete heart block is reviewed and a case is reported in which an infant was born with complete heart block. An associated anomaly was suspected but was not elaborated upon. It was also noted that one sibling had complete heart block and had died at the age of 3 years with an infectious disease. Four other siblings were normal.

SHEPS

Fisher, J. M., and Van Epps, E. F.: Aplasia or Hypoplasia of One Pulmonary Artery: Radiologic and Pulmonary Function Studies. Am. Heart J. **58:** 26 (July), 1959.

Seven patients with hypoplasia or unilateral absence of a main branch of the pulmonary artery are reported. In each the diagnosis was made before autopsy or surgical exploration. All the patients in this series were relatively asymptomatic except for mild exertional dyspnea and respiratory infections. Most of the patients showed a loud systolic murmur in the pulmonic area or along the left sternal border. This murmur was thought to arise from dilatation and tortuosity of the patent pulmonary artery. In 1 patient the murmur led to a mistaken diagnosis of heart disease and the imposition of needless restrictions. The authors point out that the diagnosis of this condition is initially a radiographic one and the radiologist should be aware of it. In most instances careful study of the pulmonary vasculature in the plain chest film should suggest hypoplasia or agenesis of a pulmonary artery. Angiocardiography should be reserved for those patients with associated lung disease that obscures the pulmonary vessels. The reported pulmonary function studies in this condition are reviewed and additional data in 3 of the patients of this series presented. There was no evidence of pulmonary insufficiency for oxygenation or elimination of carbon dioxide. In 2 the lung volumes were normal and in the third patient the reduced lung volume probably was due to associated bronchiectasis. All patients hyperventilated at rest and had decreased P_{CO_2} with normal arterial P_{CO_2}. Anatomically, agenesis of a pulmonary artery has been associated with complete absence of the lung but more commonly has been associated with hypoplasia of the lung, and hypoplasia of a pulmonary artery has always been associated with a maldevelopment of the lung.

SAGALL

Kriehuber, E., and Karnell, J.: The Electrocardiogram in Coarctation of the Aorta and Its Significance in Differential Diagnosis. Cardiologia **35:** 192, 1959.

Electrocardiographic findings in 172 patients with coaretation of the aorta including 72 with additional cardiovascular abnormalities, and of 67 patients after surgical correction of the coarctation (without other cardiovascular abnormalities) are reported. In cases of isolated coaretation, no characteristic electrocardiograms were found. Signs of more advanced left ventricular strain were only encountered in middle age or later, but in themselves were not pathognomonic for coaretation. When signs of advanced left ventricular strain were found in patients under 20, combination with subaortic stenosis was almost invariably present. In this age group, such findings are thus highly suggestive of such a combination or of associated valvular stenosis.

BRACHFELD

Neill, C. A., and Taussig, H. B.: Indications and Contraindications for Surgery in Ventricular Septal Defect. J. Pediat. **55:** 374 (Sept.), 1959.

In this article the authors reviewed and discussed the pathologic physiology of the pulmonary vascular tree in patients with varying sizes of ventricular septal defects both with and without pulmonary hypertension. They concluded that patients with small ventricular septal defects and small left-to-right shunts should not have surgery performed at the present time, that patients with moderate left-to-right shunts and mild or moderate pulmonary hypertension should have their defects repaired, that patients with large left-to-right shunts and severe pulmonary hypertension should have surgery (if clinically feasible) in early childhood and, rarely, in infancy, and finally that patients with Eisenmenger's complex should be denied surgery at least until our understanding of the postoperative management of pulmonary hypertension is improved.

KARPMAN

Portillo, B., Espino Vela, J., Del Rio, R., and Soni, J.: Truncus and Hemitruncus. Arch. Inst. cardiol. de México **29:** 100 (Jan.-Feb.), 1959.

Fourteen clinical cases of persistent common arterial trunk are presented. The clinical features

are described with emphasis on the distinctive clinical, radiologic, and electrocardiographic elements of this malformation that differentiate it from some of the other cyanotic malformations. The authors' experience with the angiocardiographic study of 2 cases is described as well as the hemodynamic findings in 4 cases.

BRACHFELD

Wright, F. S., Adams, P., Jr., and Anderson, R. C.: Congenital Atrioventricular Dissociation due to Complete or Advanced Atrioventricular Heart Block. J. Dis. Child **98**: 72 (July), 1959.

Twelve children with complete or advanced atrioventricular block (all presumably congenital) but without associated cardiac malformations were studied clinically and by cardiac catheterization. Symptomatology was generally minimal but occasionally was quite severe (i.e., cyanosis, syncope, pallor); systolic murmurs were present in all cases and, rarely, were accompanied by a diastolic murmur. Cardiac catheterization in several cases revealed the presence of an elevated right ventricular pressure, decreased systemic blood flows and normal stroke outputs. Atrioventricular block was found in 3 siblings of 1 family. The authors concluded that the favorable outlook for patients with congenital heart block is due to the fact that most cases are caused by atrioventricular dissociation with advanced atrioventricular block; under these circumstances, one might expect ventricular capture to occur whenever the lower pacemaker becomes unduly slow, thereby preventing Stokes-Adams attacks.

KARPMAN

CONGESTIVE HEART FAILURE

Bertelli, G., Di Perri, T., and Fabrizi, G.: Behavior of the Electric Systole in Congestive Heart Failure and during Recompensation. Arch. mal. coeur. **52**: 926 (Aug.), 1959.

In 48 cardiac patients in congestive heart failure the duration of the Q-T interval was always prolonged when compared to normal values for the heart rate. After recompensation, which was usually brought about by bed rest and 3 to 5 days of fasting, the Q-T interval became nearly normal regardless of the behavior of the heart rate. These findings are explained by an increase in intracellular sodium and decrease in intracellular potassium of the heart muscle cell in cardiac failure, and the correction of this abnormal distribution by the complete absence of dietary sodium during the period of treatment.

LEPESCHKIN

Bodi, T., Fuchs, M., Irie, S., and Moyer, J. H.: Further Observations on Flumethiazide. A New Oral Diuretic Agent. Am. J. Cardiol. **4**: 461 (Oct.), 1959.

The administration of flumethiazide in single doses up to 2,000 mg. did not significantly alter renal function tests in 7 hospitalized cardiac patients who had no evident renal disease. This observation suggests that its diuretic effect results from inhibition of tubular reabsorption (of sodium and water). The administration of flumethiazide 1,600 to 2,000 mg. daily for 6 days to 16 patients with compensated arteriosclerotic heart disease was attended by pronounced parallel increase in sodium and water excretion, which reached a peak within 2 days and returned to control levels 2 or 3 days later. Significant effects on potassium excretion were not observed. The diuretic efficacy and minimal kaliuretic effect make flumethiazide a valuable drug for treatment of the edematous patient.

ROGERS

Stuart-Harris, C. H.: A Hospital Study of Congestive Heart Failure with Special Reference to Cor Pulmonale. Brit. M. J. **2**: 201 (Aug. 22), 1959.

Pulmonary heart failure was investigated as the etiologic factor in a group of 487 patients with congestive heart failure admitted to a group of regional hospitals. The over-all prevalence of cor pulmonale in this group was 35 per cent. There was a distinct preponderance in males aged 45 to 64, but patients over 70 were not included in the study. Past attacks of bronchitis and pneumonia were common in this group. Expectoration of mucopurulent sputum, drowiness or disorientation, cyanosis of the lips or tongue, clubbing of the fingers, emphysema, and right ventricular disease were common to patients with cor pulmonale. In addition, when cor pulmonale was present, a raised hematocrit value and a high plasma alkali reserve were commonly found and, furthermore, residence in an industrial environment was frequently elicited in the history. However, atrial fibrillation, left ventricular disease, and hypertension occurred in a low incidence.

KRAUSE

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N.Y.
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Association Allocates $1,812,885 To Support 176 Investigators

The Association has awarded $1,812,885 through its national research program to provide 176 investigatorships and fellowships during the fiscal year beginning July 1, 1960. Also included in the awards were increases in stipends based on the rising cost of living.

Another group of national awards, in the Grant-in-Aid category, will be announced in the near future. In addition, state and local affiliates of the Association make direct awards to investigators in their areas.

The new allocations include funds for seven Career Investigators, 96 new and continued Established Investigators, 44 new and continued Advanced Research Fellows and 29 new and continued Research Fellows.

This year's sum for investigatorships, largest in the Association's history, represents an increase of more than $250,000 over amounts awarded for that purpose last year. Stipends were increased as follows: Established Investigators, from a previous range of $6500-$8500, to a present range of $7500-$9900 plus dependency allowance; Advanced Research Fellows, from $4600-$5000 to $5500-$6000; and Research Fellows, from $3800-$4200 to $4000-$4500. In addition, dependency allowances were increased for Advanced Research Fellows and Research Fellows.

A complete list of recipients of the present awards appears at the end of this section.

Bio-Science Agency Analyzes Heart Association's Research

To make possible better evaluation of their research programs and stimulate the interchange of scientific information, affiliates and chapters of the American Heart Association are now registering their research awards through the Bio-Sciences Information Exchange (BSIE), government clearing house for biological and medical research.

BSIE has assisted in evaluating the Association's national research programs for the past decade. Under the new arrangement, all research awards made by affiliated Heart Associations after July 1, 1959 in amounts of $1500 or more, will be reported for analysis to the BSIE through the AHA National Office.

Abstracts of Papers Due June 1 For AHA Scientific Sessions

Those wishing to present papers at the annual Scientific Sessions of the American Heart Association in St. Louis, October 21-23, may now obtain official forms for the submission of abstracts. Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less including a brief digest of the results obtained and conclusions reached. All applications received will be screened by the AHA Committee on Scientific Sessions Program.

Official forms for submitting abstracts as well as applications for *scientific* exhibit space may be obtained from F. J. Lewy, M.D., Assistant Medical Director, American Heart Association. These must be returned postmarked no later than June 1, 1960.

Space for *industrial* exhibits may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, New York.

Additional Affiliate Funds Aid National Research Program

The Mississippi Valley Heart Council, a chapter of the Iowa Heart Association, has provided $1500 to supplement the Association's national research support program for the 1959-60 fiscal year, bringing to $68,680 the allocations made by affiliates and chapters for this purpose through January, 1960. These sums were contributed in addition to amounts regularly assigned by Heart Associations for national research.

Coronary Atherosclerosis Book Updated by Association

The Association's booklet, "Heart Disease Caused by Coronary Atherosclerosis," for distribution by physicians to their heart patients, has been completely revised to bring the text and illustrative material up to date. Contents include a discussion of heart attacks and the process of recovery, an explanation of the nature and treatment of angina pectoris, and a description of the atherosclerotic process underlying heart attacks and angina pectoris. Copies may be obtained without charge from local Heart Associations or the American Heart Association.

Meetings Calendar

April 13: Symposium on Current Concepts of Lipid Metabolism, Federation of American Societies for Experimental Biology, Chicago. M. O. Lee, 9650 Wisconsin Avenue, N.W. Washington 14, D.C.

May 1-2: American Society for Clinical Investigation, Atlantic City, S. J. Farber, 550 First Ave., New York 16, N. Y.

May 3-4: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 11-13: American Association for Thoracic Surgery, Miami Beach. H. T. Langston, 7730 Carondelet Ave., St. Louis 5, Mo.

May 23-28: American College of Cardiology, Indianapolis. Philip Reichert, 2709 Empire State Bldg., New York 1, N. Y.

June 8-12: American College of Chest Physicians, Miami Beach. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Ill.

June 11: International Cardiovascular Society, North American Chapter, Miami Beach. P. T. DeCamp, 3503 Prytania St., New Orleans 15, La.

June 12: Society for Vascular Surgery, Miami Beach. G. H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Md.

June 13-17: American Medical Association, Annual Meeting, Miami Beach. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

August 8-11: National Medical Association, Pittsburgh. John T. Givens, 1108 Church Street, Norfolk, Va.

August 21-26: International Congress of Physical Medicine, Washington, D. C. W. J. Zeiter, 2020 E. 93rd St., Cleveland, Ohio.

August 28-September 3: International Society for Welfare of Cripples, 8th World Congress, New York. Donald V. Wilson, 701 First Ave., New York 17, N. Y.

September 11-15: International College of Surgeons, New York. Max Thorek, 850 W. Irving Park Road, Chicago 13, Ill.

September 27-30: American Roentgen Ray Society, Atlantic City. Hugh Jones, 20 N. Wacker Drive, Chicago 6, Ill.

October 10-14: American College of Surgeons, Clinical Congress, San Francisco. W. E. Adams, 40 E. Erie Street, Chicago 11, Ill.

October 21-25: American Heart Association, Annual Meeting and Scientific Sessions (October 21-23), St. Louis. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 31-November 2: Association of American Medical Colleges, Hollywood Beach, Fla. Ward Darley, 2530 Ridge Ave., Evanston, Ill.

October 31-November 4: American Public Health Association, San Francisco. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

Abroad

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Ave., New York 22, N. Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmasse, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

May 30-June 3: Asian-Pacific Congress of Cardiology, Melbourne, Australia. A. E. Doyle, Alfred Hospital, Melbourne, S. 1, Victoria, Australia.

June 2-4: International Symposium on Drugs Affecting Lipid Metabolism. Milan, Italy. Prof. S. Garattini, Institute of Pharmacology, Via A. del Sarto 21, Milan, Italy.

August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

August 24-27: International Congress of Intern[illegible]

Medicine, Basel, Switzerland. Secretariat, 13 Steinentorstre, Basel, Switzerland.

August 28-September 1: International Congress of Diseases of the Chest, Vienna. Murray Kornfeld, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Ill.

September 1-4: First International Congress of Nephrology, Geneva and Euian, France. G. Richet, 149 Rue de Sevres, Paris 15, France.

September 4-10: International Society of Hematology, Tokyo. J. L. Tullis, 1180 Beacon Street, Brookline 46, Mass.

September 18-25: European Congress of Cardiology, Rome. V. Puddu, Clinica Medica, University of Rome, Italy.

1962:

October: Fourth World Congress of Cardiology, Mexico City. I. Chavez. Ave. Cuauhtemoc 300, Mexico, D. F.

AHA Award Recipients

Following is a list of investigators who will be supported during the fiscal year beginning July 1, 1960 by the American Heart Association:

Career Investigators

Coons, Albert H., Harvard University Medical School, Boston.

Lorber, Victor, University of Minnesota Medical School, Minneapolis.

Pappenheimer, John R., Harvard University Medical School, Boston.

Sprinson, David B., Columbia University College of Physicians and Surgeons, New York.

Taggart, John V., Columbia University College of Physicians and Surgeons, New York.

Wannamaker, Lewis W., University of Minnesota Medical School, Minneapolis.

Zilversmit, Donald B., University of Tennessee College of Medicine, Memphis.

Continued Established Investigators

Albrink, Margaret J. Effect of metabolic and nutritional factors on serum lipids. Yale University School of Medicine, New Haven, Conn.

Benesch, Reinhold. Role of sulfhydryl and disulfide groups in biological systems. Marine Biological Laboratory, Woods Hole, Mass.

Boyle, Edwin, Jr. Comparative studies in lipoprotein transport and metabolism concerning atherosclerosis in man, monkeys and pigs. Medical College of South Carolina, Charleston.

Brewster, William R., Jr. Hemodynamic and metabolic interrelationships and mechanism of action of the thyroid hormones, sympathoadrenal hormones, and the adrenal cortical steroids. J. Hillis Miller Health Center, University of Florida College of Medicine, Gainesville.

Bricker, Neal S. Pathological physiology of chronic Bright's disease. University of Copenhagen, Denmark.

Combes, Burton. Hepatic metabolism during hepatoportal hemodynamic adjustments. University of Texas Southwestern Medical School, Dallas.

Daly, Marie M. Arterial metabolism in hypertension. Albert Einstein College of Medicine of Yeshiva University, New York.

DuBois, Arthur B. Gas exchange in the lungs, mechanics of breathing and pulmonary capillary blood flow. University of Pennsylvania Graduate School of Medicine, Philadelphia.

Eckstein, John W. Venomotor responses to circulatory alterations in man. State University of Iowa College of Medicine, Iowa City.

Epstein, Franklin H. Metabolic and circulatory factors affecting the distribution and excretion of water and electrolytes. Yale University School of Medicine, New Haven, Conn.

Farrell, Gordon L. Physiological factors which regulate the secretion of aldosterone. Western Reserve University School of Medicine, Cleveland.

Finnerty, Frank A., Jr. Further studies on the pathogenesis of toxemia of pregnancy and other types of acute hypertension. District of Columbia General Hospital, Washington, D. C.

Flavin, Martin, Jr. Enzyme chemistry and intermediary metabolism. National Heart Institute, Bethesda, Md.

Foulkes, Ernest C. Fundamental mechanisms of electrolyte transport across biological membranes. May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Fresco, Jacques R. Macromolecular aspects of nucleic acid structure and function. Princeton University, Princeton, N. J.

Gamble, James L., Jr. Mitochondrial function in relation to electrolyte transport. Johns Hopkins University School of Medicine, Baltimore.

Gibson, David M. Enzymatic synthesis of fatty acids in animal tissues. Indiana University School of Medicine, Indianapolis.

Gidez, Lewis I. Factors determining serum lipid composition and concentration. Albert Einstein College of Medicine of Yeshiva University, New York.

Giebisch, Gerhard. Ion transport across renal tubules of the amphibian and mammalian kidney, utilizing micropuncture techniques. Cornell University Medical College, New York.

Gilbert, James B. Role and site of binding of the metal ion in metal-containing or metal-activated enzymes. Clayton Foundation, Biochemical Institute, University of Texas, Austin.

Gitlin, David. Blood and tissue proteins. Harvard Medical School, Boston.

Goldthwait, David A. Biosynthesis of purine nucleotides and of ribonucleic acid. Western Reserve University School of Medicine, Cleveland.

Gottschalk, Carl W. Micropuncture study of kidney function. University of Copenhagen, Denmark.

Gross, Jerome. Structure, composition, genesis, function and malfunction of connective tissues. Massachusetts General Hospital, Boston.

Havel, Richard J. Mechanisms of lipid transport and the relation of altered lipid transport to atherogenesis. University of California Medical Center, San Francisco.

Henly, Walter S. Determination of myocardial blood flow in the intact subject, utilizing radioiodinated (I^{131}) human serum albumin. Baylor University College of Medicine, Houston.

Huckabee, William E. Metabolic reactions to circulatory disturbances and their role in the control of the circulation. Massachusetts Memorial Hospitals, Boston.

Jacobs, Earl E. Structural factors involved in mitochondrial oxidative phosphorylation mechanisms. Dartmouth Medical School, Hanover, N. H.

Kaplan, Melvin H. Localization of tissue-deposited streptococcal antigens and antibodies in animal and human tissues by means of the fluorescein-labeling technique; pathogenesis of rheumatic fever and rheumatic heart disease in relationship to the autoimmune theory of pathogenesis. Cleveland Metropolitan General Hospital, Cleveland.

Katz, Yale J. Renal revascularization in experimental hypertension and renal insufficiency. University of Southern California School of Medicine, Los Angeles.

Khairallah, Philip A. Reactivity of blood vessels. Cleveland Clinic, Cleveland.

Kun, Ernest. Pathway of the metabolism of hydroxy acids. University of California Medical Center, San Francisco.

Kuo, Peter T. Intravascular distribution of lipid particles in clinical arteriosclerosis. Hospital of the University of Pennsylvania and University of Pennsylvania School of Medicine, Philadelphia.

Lazzarini, Abel A., Jr. Metabolic and immunological changes occurring in transplanted tissues. New York University Post-Graduate Medical School, New York.

Lewis, David H. Regulation of the circulation in man. Philadelphia General Hospital, Philadelphia.

Linker, Alfred. Mucopolysaccharides. Columbia University College of Physicians and Surgeons, New York.

Mann, George V. Cause and prevention of atherosclerosis. Vanderbilt University School of Medicine, Nashville.

Martin, Harry B. Surface tension as a factor in the mechanical properties of normal and abnormal lungs. Harvard University School of Public Health, Boston.

Morgan, Richard S. Ribonucleic acid structures. Brandeis University, Waltham, Mass.

Nelson, Clifford V. I. Mechanism of fibrillation. II. Quantitation of the vectorcardiogram. Maine Medical Center, Portland.

Padawer, Jacques. Physiology of the mast cell and its relation to cardiovascular function and disease. Albert Einstein College of Medicine of Yeshiva University, New York.

Page, Ernest. Ion fluxes in mammalian heart muscle. Harvard Medical School, Boston.

Perry, H. Mitchell, Jr. Pathogenesis and treatment of hypertension and atherosclerosis. Washington University School of Medicine, St. Louis.

Pick, Ruth. Pathogenesis of atherosclerosis and its sequelae. Medical Research Institute, Michael Reese Hospital, Chicago.

Pollak, Victor E. Investigations on the kidney in health and disease. University of Illinois College of Medicine, Chicago.

Portman, Oscar W. Dietary factors affecting cholesterol catabolism and atherosclerosis. Harvard University School of Public Health, Boston.

Richmond, Jonas E. Role of the prosthetic group of proteins in the biosynthesis and metabolism of conjugated proteins. Harvard Medical School, Boston.

Rudolph, Abraham M. Pulmonary hypertension in congenital heart disease. Albert Einstein College of Medicine of Yeshiva University, New York.

Schmidt-Nielsen, Bodil M. Comparative kidney physiology. Duke University, Durham, N. C.

Schwartz, William B. Disorders of electrolyte metabolism and kidney function. New England Center Hospital, Boston.

Shumway, Norman E., Jr. Ventricular fibrillation by threshold determinations. Stanford University, School of Medicine, Palo Alto, Cal.

Slade, Hutton D. Biochemistry of the group A hemolytic streptococcus. Northwestern University Medical School, Chicago.

Spencer, Merrill P. Factors affecting distribution of cardiac output. Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Springer, Georg F. Plant polysaccharides in relation to lipemia clearing, coagulation, blood group specificity and the infectious mononucleosis. Hospital of the University of Pennsylvania, Philadelphia.

Staple, Ezra. Metabolism of cholesterol, mechanisms of synthesis and breakdown of related substances. University of Pennsylvania School of Medicine, Philadelphia.

Straus, Werner. Investigation of "phagosomes" in various tissues of the rat. University of Louvain, Belgium.

Szent-Gyorgyi, Andrew G. Structure of myosin. Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass.

Thal, Alan P. I. Revascularization of the myocardium; experimental study designed to test the feasibility of a direct suture anastomosis of extracardiac arteries to the coronary arteries. II. Mechanism of action of bacteria and bacterial toxins on small

blood vessels with particular reference to bacterial shock. University of Minnesota Medical School, Minneapolis.

Thomas, Randall H. Hydrocortisone metabolism in diabetes mellitus. University Hospitals of Cleveland and Western Reserve University School of Medicine, Cleveland.

Tsuboi, Kenneth K. Metabolism of nucleotides and related compounds in cardiac tissues. Stanford University School of Medicine, Palo Alto, Calif.

Ulrich, Frank. Metabolic fate and mechanism(s) of action of adrenal cortical hormones in the peripheral tissues. Yale University School of Medicine, New Haven, Conn.

Vernier, Robert L. Etiology and pathogenesis of diffuse cardiovascular disease in childhood. University of Minnesota Medical School, Minneapolis.

Walker, W. Gordon. I. Plasma protein metabolism, capillary protein permeability and circulatory homeostasis. II. Hyponatremia in congestive heart failure. III. Electrolyte permeability in the gut. Johns Hopkins Hospital, Baltimore.

Warner, Homer R. Application of analogue computer techniques to the study of regulation of the circulation. University of Utah College of Medicine and Latter-Day Saints Hospital, Salt Lake City.

New Established Investigators

Bloomfield, Daniel K. Comparative enzymology of the conversion of cholesterol to bile acid. Western Reserve University School of Medicine, Cleveland.

Briggs, F. Norman. Muscle relaxation—biochemical studies. Tufts University School of Medicine, Boston.

Cooper, David Y. Steroid formation in essential hypertension. University of Pennsylvania School of Medicine, Philadelphia.

DeWall, Richard A. Perfusion techniques as applied to open cardiac surgery. University of Minnesota Medical School, Minneapolis.

Dickerman, Herbert W. Basic amino acid transport and metabolism in the kidney. Johns Hopkins University School of Medicine, Baltimore.

Elwyn, David H. Quantitative aspects of amino acid metabolism. Michael Reese Hospital, Chicago.

Feinberg, Harold. Myocardial metabolism and cardiac dynamics. Medical Research Institute, Michael Reese Hospital, Chicago.

Gentsch, Thomas O. I. Remote stimulation by radio frequency transmission. II. Development of a vertical membrane oxygenator and the effects of extracorporeal bypass on the heart. Yale University School of Medicine, New Haven, Conn.

Hamerson, Irwin B. Relationship of the kidney, liver and adrenal glands to arterial hypertension. May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Hatch, Frederick T. Biosynthesis and degradation of lipoproteins. Massachusetts General Hospital, Boston.

Hougie, Cecil. Blood clotting and fibrinolytic enzyme systems. University of Virginia School of Medicine, Charlottesville.

Maley, Gladys F. Interconversions of nucleotides in embryonic and neoplastic tissues. New York State Department of Health, Albany.

Markus, Gabor. Clinical and biochemical studies on the fibrinolytic system in man. Roswell Park Memorial Institute, Buffalo, N. Y.

Mueller, Helmut. Characterization of the relaxing factor and its interaction with contractile proteins. University of Birmingham, England.

Savitsky, J. Philip. Metabolic regulatory effects of desoxyribonucleic acids. Montefiore Hospital, New York.

Ziegler, Daniel M. Mitochondrial electron transport system. Institute for Enzyme Research, University of Wisconsin, Madison.

Continued Established Investigator-Grantees

Conway, F. James. Aging of arteries in relation to hypertension. University of Michigan Medical School, Ann Arbor.

Corcoran, John W. Metabolism of the branched chain monosaccharides and their role in the mammalian and bacterial cell. Western Reserve University School of Medicine, Cleveland.

Despopoulos, Agamemnon. Parameters of cellular transport phenomena. University of Louisville School of Medicine, Kentucky.

Durbin, Richard P. Transport of water and HCl by the stomach. Harvard Medical School, Boston.

Goldstein, Robert. Isolation and identification of prothrombin and "serum factors;" investigation of their role in coagulation and thrombosis. New England Center Hospital, Boston.

Landau, Bernard R. Carbohydrate metabolism in hyperthyroidism. Western Reserve University School of Medicine, Cleveland.

Rubin, Albert L. Investigation of the metabolic alterations in the uremic syndrome. Cornell University Medical College and New York Hospital, New York.

New Established Investigator-Grantees

Brady, Allan J. Link between excitation and contraction. University of California Medical Center, Los Angeles.

Clayton, Raymond B. Function and utilization of sterols in insects. Harvard University, Cambridge, Mass.

Dallam, R. Duncan. Cellular chemistry and bioenergetics. University of Louisville School of Medicine, Kentucky.

Gubler, Clark J. Enzymatic functions of thiamin. Brigham Young University, Provo, Utah.

Harris, John B. Interrelationships between bioelec-

trical properties and electrolyte transport. University of California School of Medicine, San Francisco.

Hefner, Lloyd L. Relationships between heat production, oxygen consumption and work of the mammalian heart. Medical College of Alabama, Birmingham.

Hirschhorn, Kurt. Genetic and metabolic aspects of atherosclerosis. New York University Post-Graduate Medical School, New York.

Watanabe, Shizuo. Mechanism of relaxation of glycerol-treated muscle fibers. Dartmouth Medical School, Hanover, N. H.

Wilson, Jean D. Mechanism of neutral sterol secretion into the gut. University of Texas Southwestern Medical School, Dallas.

Continued Advanced Research Fellows

Burack, W. Richard. Isolation of vasoactive substance(s) from normal and damaged myocardium. Under Paul B. Hagen, Harvard Medical School, Boston.

Cayler, Glen G. Longitudinal study of hemodynamic and pulmonary vascular changes in the full-term and premature puppy. Under Robert H. Bayley, University of Oklahoma School of Medicine, Oklahoma City.

Goodkind, M. Jay. Myocardial metabolism in normal and hyperkinetic states. Under Allan V. N. Goodyer, Yale University School of Medicine, New Haven, Conn.

Greenberg, Wayne V. Role of growth hormone in lipid metabolism and atherogenesis. Under Kenneth R. Crispell, New York Medical College, New York.

Javitt, Norman B. Patterns of proteinuria in chronic renal disease. Under Stanley E. Bradley, Columbia University College of Physicians and Surgeons, New York.

Katz, Joseph. Mechanism and site of plasma protein breakdown. Under Alvin L. Sellers, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.

Lacy, William W. Metabolism in uremia. Under Elliott V. Newman, Vanderbilt University School of Medicine, Nashville, Tenn.

Nathan, Paul. Kidney transplantation. Under Benjamin F. Miller, May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Peifer, James J. Chemistry and metabolism of lipids related to heart disease. Under Walter O. Lundberg, Hormel Institute, University of Minnesota, Austin.

Radding, Charles M. Biochemical basis of genetics. Under Arthur Kornberg, Stanford University School of Medicine, Palo Alto, Calif.

Rakita, Louis. Nature of myocardial hypertrophy: transmembrane potential, intramural potential, and histochemical alterations in myocardial muscle associate with ventricular hypertrophy. Under Charles H. Rammelkamp, Jr., Cleveland Metropolitan General Hospital, Ohio.

Reeves, John T. Oxygen transport and the pulmonary circulation at rest and during exercise in normal and pathological subjects. Under S. Gilbert Blount, Jr., Colorado General Hospital and University of Colorado School of Medicine, Denver.

Rosa, Leslie M. Chest accelerograms and vibrocardiograms in coronary heart diseases. Under Aldo A. Luisada, Chicago Medical School.

Spiro, Robert G. Composition and structure of the carbohydrate moiety of the glycoprotein of fetal calf serum. Under Roger W. Jeanloz, Massachusetts General Hospital, Boston.

Stanfield, Calvin A. Effects of exercise and various pharmacological agents on pulmonary circulation and ventricular function. Postgraduate Medical School, London, England.

Stoffyn, Pierre J. Chemistry and biochemistry of heparin. Under Roger W. Jeanloz, Massachusetts General Hospital, Boston.

Taranta, Angelo. Secondary immune response—reinvestigation. Studies on Sydenham's chorea. Under Harrison F. Wood, Irvington House, Irvington-on-Hudson, N. Y.

Tuna, Naip. Fatty acids and atherosclerosis. Under Ivan D. Frantz, Jr., University of Minnesota Medical School, Minneapolis.

Vance, Vernon K. Adrenal inhibition in edematous states. Under George W. Thorn, Peter Bent Brigham Hospital, Boston.

Welsh, Richard S. Characterization of an undegraded, nonfibrous form of desoxyribonucleoprotein from calf thymus. Under George J. Hollenberg, University of Redlands, Redlands, Calif.

New Advanced Research Fellows

Abboud, Francois M. Effect of cold air inhalation on normal and abnormal pulmonary circulations. State University of Iowa, College of Medicine, Iowa City.

Adamis, Dionysios. Development of thrombolytic and anticoagulating agents from molds and plants. Under Mario Stefanini, Saint Elizabeth's Hospital, Boston.

Bowman, Roger H. Normal and fasting metabolism of cardiac muscle and the hormonal influences involved. Under F. G. Young, University of Cambridge, England.

Carrasquer, Gaspar. Electrolyte and water function of the kidney; mechanism of tubular ion transport and acidification of the urine. Under William A. Brodsky, University of Louisville School of Medicine.

Cohen, Louis. Phospholipid composition of serum lipoproteins and the coagulant activity of serum phospholipids in health and coronary artery disease.

Under Richard J. Jones, University of Chicago School of Medicine.

Cummings, Nancy B. Alterations in metabolism in renal disease. Under DeWitt Stetten, Jr., National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.

Derks, Miriam A. Function of N-acetylamino derivatives in metabolism. Under Luis F. Leloir, Instituto de Investigaciones Bioquimicas, Buenos Aires, Argentina.

Ells, H. Alan. Effects of quinidine on carbohydrate metabolism. Under Robert H. Furman, Oklahoma Medical Research Foundation, Oklahoma City, Okla.

Glagov, Seymour. Distribution of atherosclerosis in the major arteries as a function of altered circulatory conditions in the supplied organs. Under Donald A. Rowley, University of Chicago School of Medicine.

Hall, Philip W., III. Water and electrolyte balances in patients with refractory edema. Under George J. Gabuzda, Cleveland Metropolitan General Hospital.

Hays, Richard M. Mechanism of action of antidiuretic hormone. Under Irving M. London, Albert Einstein College of Medicine of Yeshiva University, New York.

Hess, Marilyn E. Influence of hormones on the enzymatic and functional activity of heart muscle. Under Niels Haugaard, University of Pennsylvania School of Medicine, Philadelphia.

Jensen, David. Basic mechanisms of cardiac automatism. Under Per F. Scholander, University of California, Scripps Institution of Oceanography, La Jolla, Calif.

Lauler, David P. I. Nephron population in acute renal failure. II. Blood-cerebrospinal fluid barrier in uremia. III. Effect of low salt diet on renal function in chronic renal disease. Under John P. Merrill, Peter Bent Brigham Hospital, Boston.

Maffly, Roy H. Isolation of the sodium bound by the actively transporting toad bladder. Under Isidore S. Edelman, University of California Medical Center, San Francisco.

Miller, Tracy B. Hyaluronidase and the action of the antidiuretic hormone. Under Alfred E. Farah, State University of New York Upstate Medical Center, Syracuse, N. Y.

Peters, John H. Immunologic aspects of connective tissue and diseases of "hypersensitivity." Under Albert H. Coons, Harvard Medical School, Boston.

Ronwin, Edward. Enzymes involved in blood clotting and fibrinolysis; biochemical characterization of the processes. Under George P. Hager, University of Minnesota College of Pharmacy, Minneapolis.

Said, Sami I. Gas exchange and the pulmonary capillary circulation. Under John L. Patterson, Jr., Medical College of Virginia, Richmond.

Shabetai, Ralph. Effects of pharmacologic agents on the pulmonary circulation. Under Noble O. Fowler, Cincinnati General Hospital, Cincinnati.

Shneour, Elie A. Biosynthesis of carotenoids in nonsulfur purple bacteria. Under Roger Y. Stanier, University of California, Berkeley.

Walker, James E. C. Effect of cold on patients with angina pectoris. Under Roe E. Wells, Jr., Peter Bent Brigham Hospital, Boston.

Wexler, Bernard C. Pathology and endocrinology of arteriosclerosis in the rat. Under Benjamin F. Miller, May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Yaffe, Sumner J. Metabolic basis for the renal concentrating mechanism. Under Norman Kretchmer, Stanford University School of Medicine, Palo Alto, Calif.

Continued Research Fellows

Baskys, Bronius. In vitro studies of the effects of various lipases on the serum lipoproteins in normal individuals and in patients with idiopathic hyperlipemia and primary hypercholesteremia. Under Walter F. Lever, Tufts University School of Medicine, Boston.

Constantine, Herbert P. Diffusion capacity of the lung and its relationship with the pulmonary circulatory dynamics. Under Nolan Kaltreider and Paul N. Yu, University of Rochester Medical Center, Rochester, N. Y.

Fekete, Laszlo, L. Relation of inhibition of lipemia clearing to disturbed lipid transport. Under Walter F. Lever, Tufts University School of Medicine, Boston.

Griege, Charles W. Coronary circulation and cardiac metabolism in normal and pathological conditions. Under René Wégria, St. Louis University School of Medicine, St. Louis.

MacLeod, Robert M. Relationships of cell structure to cell function. Under William S. Lynn, Duke University School of Medicine, Durham, N. C.

Morrin, Peter A. F. Pathological physiology of Bright's disease. Under Neal S. Bricker, Barnes Hospital, St. Louis.

Utley, James H. Coronary circulation and cardiac metabolism under normal and pathological conditions. Under René Wégria, St. Louis University School of Medicine, St. Louis.

Warwick, Warren J. Delayed type bacterial allergy. Under Robert A. Good, Heart Hospital and University of Minnesota Medical School, Minneapolis.

Williams, John F., Jr. Cardiac response of patients with pulmonary emphysema to exercise and venesection. Under Roy H. Behnke, Veterans Administration Hospital and Indiana University Medical Center, Indianapolis.

New Research Fellows

Arky, Ronald. Carbohydrate metabolism in uremia. Under Albert L. Rubin, Second Cornell Medical Division, Bellevue Hospital, New York.

Blaquier, Pedro C. Relation of renin and angiotensinase content of the kidney to the development of hypertension. Under David F. Bohr, University of Michigan Medical School, Ann Arbor.

Bresler, Howard L. Oxygen relationship to pulmonary hypertension. Under Peter V. Moulder, University of Chicago School of Medicine, Chicago.

Criley, John Michael. I. Exaggerated natriuresis in congenital heart disease. II. Clinical-physiological correlations in cardiovascular disease. Under E. Cowles Andrus and Richard S. Ross, Johns Hopkins Hospital, Baltimore.

Finn, Arthur L. Effects of mineralocorticoids on thirst mechanisms and renal concentrating ability. Under Louis G. Welt, North Carolina Memorial Hospital, Chapel Hill.

Grant, C. Mackenzie. Method for the quantitative study of pulmonary congestion and edema. Under David G. Greene, University of Buffalo School of Medicine and Buffalo General Hospital, N. Y.

Harrison, Donald C. Pulmonary Blood Volume. Under Lewis Dexter, Peter Bent Brigham Hospital, Boston.

Hurt, Holcombe H., Jr. Relationship between pulmonary resistance to ventilation and the state of inflation of the lungs in patients with pulmonary vascular congestion. Under Richard L. Riley, Johns Hopkins University School of Hygiene and Public Health, Baltimore.

Imperial, Elias S. Role of the "Fenn effect" in the cardiac response to increased work load. Under Matthew N. Levy, St. Vincent Charity Hospital, Cleveland.

Lancestremere, Ruben G. Relationship of renal function to cardiac output in patients with Laennec's cirrhosis. Under Solomon Papper, Medical College of Virginia, Richmond.

Mahadevan, Vaidyanath. Lipids in relation to blood coagulation. Under Walter O. Lundberg, Hormel Institute, University of Minnesota, Austin.

Manis, James. Active transport of calcium by the small intestine and the effect of vitamin D. Under David Schachter, Columbia University College of Physicians and Surgeons, New York.

Morris, James J., Jr. Shock accompanying myocardial infarction — treatment and mechanism. Under Henry D. McIntosh, Duke University Hospital, Durham, N. C.

Palman, Robert S. Simultaneous measurement of the outputs of the two ventricles by means of the indicator dilution principle using two indicators. Under Gilbert E. Levinson, Seton Hall College of Medicine and Thomas J. White Cardiopulmonary Institute, B. S. Pollak Hospital for Chest Diseases, Jersey City, N. J.

Petersen, Martin J. Relationship of adenosine triphosphate and adenosine triphosphatase to active sodium transport in the mammalian kidney; effects of adrenal steroids and mercurial diuretics on this relationship. Under Isidore S. Edelman, University of California Medical Center, San Francisco.

Rainey, Robert L. Renal hemodynamics in abnormal cardiac function. Under James W. Culbertson, University of Tennessee College of Medicine, Memphis.

Sassé, Lewis. Enzymatic phosphorylation of proteins. Under Murray Rabinowitz, University of Chicago School of Medicine, Chicago.

Vagnucci, Antonio I. Diurnal cycle of renal glomerular filtration and blood flow as correlated with electrolyte excretion in normal and hypertensive subjects. Under Laurence G. Wesson, New York University Post-Graduate Medical School, New York.

CONTRIBUTORS TO THIS ISSUE

Elia M. Ayoub, M.D.

Instructor in Pediatrics, University of Minnesota, Minneapolis, Minn.

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Associate Professor of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Va.

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Clinical Professor of Medicine and Director of the Cardiovascular Section, Hahnemann Medical College and Hospital, Philadelphia, Pa.

Harold T. Mankin, M.D., M.S. (Med.)

Consultant, Section of Medicine, Mayo Clinic, Rochester, Minn.

William H. Muller, Jr., M.D.

Stephen H. Watts Professor and Chairman, Department of Surgery, University of Virginia School of Medicine; Surgeon-in-chief, University of Virginia Hospital, Charlottesville, Va.

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Senior Medical Student, Washington University School of Medicine, St. Louis, Mo.

Reuben Straus, M.D.

Director of Laboratories and Research, St. Joseph Hospital, Burbank, Calif.

Wilbur A. Thomas, M.D.

Merrill Professor and Chairman, Department of Pathology, Albany Medical College, Albany, N.Y.

Wayne Vasey, M.A.

Dean of the Graduate School of Social Work, Rutgers, The State University; Author of *Government and Social Welfare,* New York, Henry Holt and Co., 1958.

Lewis W. Wannamaker, M.D.

Professor of Pediatrics, University of Minnesota, Minneapolis, Minn. Career Investigator of the American Heart Association

W. Dean Warren, M.D.

Assistant Professor of Surgery, University of Virginia School of Medicine, Charlottesville, Va.

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Fellow in Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

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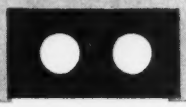
Just two tablets  *at bedtime*

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